Endo Pharmaceuticals Inc.
1400 Atwater Drive
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EN3835

EN3835-304

A PHASE 3B, OPEN-LABEL, LONG-TERM STUDY TO EVALUATE THE SAFETY AND TEMPORAL PATTERN OF RESPONSE OF EN3835 IN THE TREATMENT OF EDEMATOUS FIBROSCLEROTIC PANNICULOPATHY

IND 110077

NCT03526549

Amendment 3

Date:

Original Protocol: January 31, 2018
Amendment 1: April 19, 2018
Amendment 2: November 01, 2018
Amendment 3: January 14, 2021

The sponsor of the Investigational New Drug Application (IND) is Endo Global Aesthetics Limited (EGAL); however, Endo Pharmaceuticals Inc. (Endo) is authorized to act and to communicate on behalf of EGAL. The sponsor is responsible for the conduct of the study, analysis of the data, and preparation of the clinical study report.

Confidentiality Statement

2. SUMMARY OF CHANGES

2.1. Amendment 3

EN3835-304 protocol amendment 3 and amended informed consent forms (as necessary) have been reviewed and approved by the governing Institutional Review Boards (IRBs) before implementation of the amendment at each study center.

Amendment 3 was incorporated into the protocol on January 14, 2021. The major reason for this amendment was that the Sponsor has decided to terminate the EN3835-304 clinical trial at the completion of the 3-year time point (Day 1080). The Sponsor will offer voucher(s) for commercially approved Qwo™ redeemable only for eligible trial participant(s) who will miss their potential retreatment due to this decision. The voucher will be offered only for the intended benefit to the applicable trial participant, and will cover only the cost of the commercially approved QWO™ treatment, applicable for one course of retreatment on the participant's one or two buttocks. This voucher will be offered only if the participant is determined eligible at the 3-year study visit (Day 1080) following CR-PCSS and PR-PCSS assessments and confirmation visit to determine final eligibility.
Based on the adequate clinical safety and durability data and the long-term safety profile, Endo has concluded that the originally proposed 5 year length of the study was overestimated. Therefore, Endo has amended the protocol to end the study when all subjects have completed their 3 year (Day 1080) visit.

The major changes to the protocol are outlined below. Revisions in style, minor corrections (such as spelling errors, etc), and other minor changes that do not impact content may also have been made.

Section	Reason for Change/Original Text	Revision
Section 3 Sponsor Contact Information	Updated table to reflect new personnel in each role.	Added contact information for [redacted]
Section 4 Synopsis	Updated Study Period.	Study Period was updated to reflect a new estimated date for last subject completed of December 2021.
Section 5.3 Category I/II Subjects – Observation Assessments	Updated footnote b.	Footnote b updated to add new study termination date and the opportunity for retreatment for study subjects.
Section 10.1 and throughout the Protocol Study Design	Updated discussion of observation visits.	Observation visits have been changed from a possible 7 visits to 5 visits to reflect the change from a 5-year study to a 3-year study.
Figure 1 Study Design	Study Design Flow Chart was updated.	Study Design Flow Chart now reflects the change from a 5-year study to a 3-year study.
Section 12 and throughout the Protocol	Protocol has been updated to reflect a 3-year (36 Month, 1080 Day) design, removing all references to study visits or procedures after year 3.	References to year 4 and 5 removed.

Section	Reason for Change/Original Text	Revision
Section 18.4 Study Drug Preparation	Paragraph 2 has been updated.	Paragraph 2 was reworded to clarify the preparation, reconstitution, and storage of study drug.

2.2. Amendment 2

EN3835-304 protocol amendment 2 and amended informed consent forms (as necessary) have been reviewed and approved by the governing Institutional Review Boards (IRBs) before implementation of the amendment at each study center.

Amendment 2 was incorporated into the protocol on 01 November 2018. The major reasons for this amendment included clarifying entry criteria, clarification of Category II subject requirements for retreatment, and to allow subjects who become pregnant to continue in the observation portion of the study. The major changes to the protocol are outlined below. Revisions in style, minor corrections (such as spelling errors, etc), and other minor changes that do not impact content may also have been made.

Section	Reason for Change/Original Text	Revision
Section 3 Sponsor Contact Information	[redacted] has replaced [redacted] as the Clinical Operations Lead	[redacted] contact information added
Section 4 Synopsis		Entire synopsis updated with changes and shortened to reduce redundancy.
Section 5.1 Schedule of Events – Up to 180 Days and Section 5.2 Eligible Category I/II Subjects – Treatment Sessions Section 5.3 Category I/II Subjects – Observation Assessments Section 5.4 Category III Subjects-Assessments, Section 12.1 Study Visits	Unscheduled visits were removed from all Schedules of Events in order to allow the investigator to determine the appropriate procedures to be done at unscheduled visits and to ensure that no photographs or cellulite assessments will be done at unscheduled visits.	The Unscheduled visit column has been removed from all tables and the statement: "Unscheduled visits may be done as deemed necessary at any time during the study to ensure subject safety; assessments done at unscheduled visits are at the discretion of the investigator. No photographs or cellulite severity assessments will be done at unscheduled visits" was added to the footnotes for the tables. This statement was also added to Section 12.1. In addition, the footnotes for each table were reordered to ensure consistency and correct alphabetical order.
Section 5.1 Schedule of Events – Up to 180 Days Section 12.1.5 Day 180 Visit	Visit 1 Day 180[b] (± 14 days) M6	Visit 1 Day 180[c] (± 14 days) M6/Early Termination The following text was added to footnote[c] in the table and to the text in Section 12.1.5: A subject who terminates study participation between Day 71 and Day 180 will have an Early Termination Visit that includes the assessments listed for Visit 1 Day 180.

Section	Reason for Change/Original Text	Revision
Section 5.1 Schedule of Events - Up to 180 Days Section 14.1.1 Adverse Events		The following text has been added to footnote [n] in table and to Section 14.1.1: Any AE that occurs between the completion of studies EN3835-302/303 and the Day 180 Visit will be reported and evaluated.
Section 5.4 Category I/II Subjects – Observation Assessments Section 12.2.2.2 Visits 3-7/ EOS/Early Termination (Day 540 – Day 1800/ EOS/Early Termination		Early Termination was removed from the column header for OBS Visit 4 and added to the column header for OBS Visit 7 Day 1800 in the table. Section heading 12.2.2.2 was changed to Observation Visits 3-7/EOS/Early Termination (Day 540 – Day 1800/ EOS/Early Termination
Section 11.1.1 Inclusion Criteria – All Subjects (Through Day 180)	*The following text was deleted:* 5. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test before injection of study drug and be using a stable and effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile	
Section 11.1.2 Inclusion Criteria - Category 1 Subjects (Post Unblinding of EN3835-302/303)	*The following text was deleted:* 5. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test before injection of study drug and be using a stable and effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile.	*The following text was added:* 1. Voluntarily sign and date an informed consent agreement.

Section	Reason for Change/Original Text	Revision
Section 11.1.3 Inclusion Criteria - Category II Subjects (Post Unblinding of EN3835-302/303)	1. Received active EN3835 in study EN3835-302 or EN3835-303 2. Maximum composite response at Day 71 in either or both buttocks in double-blind study EN3835-302 or EN3835-303 was at least a 2-level composite improvement on CR-PCSS/ PR-PCSS 3. Be willing and able to cooperate with the requirements of the study 4. Be able to read, complete and understand the patient reported outcomes rating instruments in English	In order for Category II subjects to continue to participate in this study, subjects must: 1. Voluntarily sign and date an informed consent agreement. 2. Have received active EN3835 in study EN3835-302 or EN3835-303. 3. Have had a composite response at Day 71 in either or both buttocks in double-blind study EN3835-302 or EN3835-303 that was at least a 2-level composite improvement on CR-PCSS/ PR-PCSS. 4. Be willing to apply sunscreen to the buttocks before each exposure to the sun. 5. Be judged to be in good health, based upon the results of a physical examination, and laboratory profile at Screening. 6. Be willing and able to cooperate with the requirements of the study. 7. Be able to read, complete and understand the patient reported outcomes rating instruments in English.
Section 11.1.4 Inclusion Criteria – Category III Subjects (Post Unblinding of EN3835-302/303)		*The following text was added:* 1. Voluntarily sign and date an informed consent agreement.
Section 11.1.5 Inclusion Criteria – Category I and Category II Subjects Who Opt for Retreatment (Post Unblinding of EN3835-302/303)	1. Voluntarily sign and date an informed consent agreement 2. Subjects who opt for retreatment must meet one of the following criterion: a. All criteria for Category I subjects; OR b. All criteria for Category II subjects, AND must have at least one buttock that at Day 71 in double-blind study EN3835-302 or EN3835-303 was at least a 2-level composite improvement on CR-PCSS/PR-PCSS that at a subsequent visit showed at least a 1-level composite reduction of response (ie, a reduction in severity by 1-level in both the PR-PCSS and CR-PCSS) compared to the Day 71 ratings in double-blind study EN3835-302/303 in that buttock(s).	Subjects in Category I and Category II who opt for retreatment must meet the following additional inclusion criteria to be eligible for retreatment. These subjects must: 1. Voluntarily sign and date an informed consent agreement for retreatment. 2. Be willing to apply sunscreen to the buttocks before each exposure to the sun while participating in the retreatment portion of the study (ie, Treatment Visit 1 through Treatment Visit 4). 3. Be judged to be in good health, based upon the results of a physical examination, and laboratory profile at Screening. 4. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test before injection of study drug and be using a stable and effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be

Section	Reason for Change/Original Text	Revision
		menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile. 5. Category II subjects must have at least a 1-level composite response reduction compared to Day 71 of the EN3835-302/303 study AND no longer maintain a 2-level composite response compared to baseline in the EN3835-302/303 study on either or both buttocks that is confirmed at a Confirmation Visit.
Section 11.2.2 Exclusion Criteria – Category I and Category II Subjects (Post Unblinding of EN3835-302/303)	*Original Sections 11.2.2 and 11.2.3 were combined and wording updated as outlined in revised text.*	A Category I or Category II subject will be excluded from study participation if she: 1. Intends to or has used any of the following for the treatment of EFP on a buttock at any time during the course of the study: a. Liposuction in a buttock. b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock. c. Any investigational drug or treatment for EFP on a buttock (other than treatment in study EN3835-302/303). d Endermologie or similar treatments within a buttock. e. Massage therapy within a buttock during the 3 month period before observational visit. f. Creams (eg, Celluvera, TriLastin) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before observational visit. 2. Has received any collagenase treatments at any time since completion of the double-blind study 3. Any other condition(s) that, in the Investigator's opinion, might indicate that the subject is unsuitable for the study.
Section 11.2.4 Exclusion Criteria Category I and II Subjects Who Opt to Receive Retreatment (Post Unblinding of EN3835-302/303) Formerly Section 11.2.5	5. Prior to and during the course of retreatment (Treatment Visit 1 through Treatment Visit 4), is nursing or providing breast milk 6. Prior to and during the course of retreatment (Treatment Visit 1 through Treatment Visit 4), intends to become pregnant during the study	4. Is nursing or providing breast milk within 30 days prior to and/or during the course of retreatment (Treatment Visit 1 through Treatment Visit 4). 5. Is pregnant or intends to become pregnant during the course of retreatment (Treatment Visit 1 through Treatment Visit 4).

Section	Reason for Change/Original Text	Revision
Section 12.1.2 Subject Screening	*The following text has been deleted:* All potential subjects eligible for screening in EN3835-304 will be pre-populated in the electronic data capture (EDC) system. If the Screening Visit for a subject is within 14 days of the subject's Day 71 of study EN3835-302/303, the Screening Visit assessments for a subject will be pre-populated by a data transfer of the results of assessment of Day 71 (and height and Fitzpatrick scale rating of Day 1) of study EN3835-302/303 for that subject.	
Section 12.1.2 Subject Screening	If the Screening Visit for a subject is greater than 14 days of the subject's Day 71 of study EN3835-302/303, the Screening Visit assessments will be performed as detailed in Section 5.1 with only the subject ID and Fitzpatrick scale rating transferring from Day 1 of study EN3835-302/303 and pre-populating the EDC of study EN3835-304. All changes in medical history occurring between completion of study EN3835-302/303 and the Screening Visit of study EN3835-304 will be considered adverse events and will be recorded and evaluated for seriousness and severity (see as appropriate, Section 14.1.1, Adverse Events or Section 14.1.2, Serious Adverse Events).	If the Screening Visit for a subject is greater than 14 days after the subject's Day 71 of study EN3835-302/303, only the unique Screening Visit assessments will be performed (informed consent, inclusion and exclusion criteria evaluation, height, and physical examination). No subject will be allowed to enroll in the study if the Screening Visit does not occur within 180 days after Day 71 of Study EN3835-302/303. All changes in medical history occurring between completion of study EN3835-302/303 and the Screening Visit of study EN3835-304 will be considered adverse events and will be recorded and evaluated for seriousness and severity (see as appropriate, Section 14.1.1, Adverse Events or Section 14.1.2, Serious Adverse Events).
Section 12.1.3 Medical History	Since this is a long-term rollover study for subjects that participated and completed the double-blind study (EN3835-302 or EN3835-303), in which the subjects' medical history was collected; there will be no medical history collected for study EN3835-304.	Since this is a long-term rollover study for subjects that participated and completed the double-blind study (EN3835-302 or EN3835-303), in which the subjects' medical history was collected, only newly discovered medical history (events/procedures that occurred prior to enrollment in study EN3835-302/303) will be collected (eg, a subject remembers having an appendectomy as a child that was not reported in the medical history for EN3835-302/303).
Section 12.1.5 Day 180/Early Termination Visit (Screening B)	Category II subjects that have lost 1-composite level of response (ie, at least a 1-level worsening of both PR-PCSS and CR-PCSS in at least one buttock). If there is a composite worsening of cellulite severity of 1-level (ie, worsening of both the PR-PCSS and CR-PCSS by at least 1 severity levels) detected in a Category II subject, the confirmation of loss of response will be established during a follow-up visit ~2 weeks after the loss of response is detected at Day 180 as described in Section 12.2.2.3 (Confirmation Visit).	If the subject is categorized to a classification and has ratings that qualify for retreatment (ie, all Category I subjects will be offered retreatment; Category II subjects that have lost 1-composite level of response (ie, at least a 1-level composite response reduction compared to Day 71 of the EN3835-302/303 study AND no longer maintain a 2-level composite response compared to baseline in the EN3835-302/303 study on either or both buttocks). If there is a composite worsening of cellulite severity of 1-level detected in a Category II subject, the confirmation of loss

Section	Reason for Change/Original Text	Revision
		of response will be established during a follow-up visit ~2 weeks after the loss of response is detected at Day 180 as described in Section 12.2.2.3 (Confirmation Visit).
Section 12.1.5 Day 180/Early Termination (Screening B)		*The following text has been added to allow for multiple screening B visits*: If a subject does not meet Screening B criteria (eg, positive pregnancy test, elevated liver enzymes, etc), the subject maybe rescreened at a later date.
Section 12.2 Category I Subjects and Category II Subject Visits (Post Unblinding of EN3835-302/303)	Category II subjects who have shown a 1-level composite reduction of response compared to their Day 71 from EN3835-302/302 improvement will be offered a course of retreatment;…	Category II subjects who have had at least a 1-level composite response reduction compared to Day 71 of the EN3835-302/303 study AND no longer maintain a 2-level composite response compared to baseline in the EN3835-302/303 study will be offered a course of retreatment;
Section 12.2.1.2 Selecting and Marking Dimples During Treatment Visits	Category I subjects and Category II subjects eligible for retreatment can receive up to 3 retreatment visits of study drug as outlined in Section 5.2 unless the buttock is dimple-free (score of 0 on CR-PCSS as reported by the Investigator) at Treatment Visit 2 and/or Treatment Visit 3.	Category I subjects and Category II subjects eligible for retreatment can receive up to 3 retreatment visits of study drug as outlined in Section 5.2 unless the buttock is dimple-free (score of 0 on CR-PCSS as reported by the Investigator) at Treatment Visit 1, Treatment Visit 2 and/or Treatment Visit 3.
Section 13.1.2.4 Subject Satisfaction with Cellulite Treatment Assessment		*The following text was added:* The subject will view each of their pretreatment Day 1 digital images from the double-blind study (EN3835-302/303) alongside their current study visit digital images of their buttocks to aid in the assessment.
Section 14.6.3 Pregnancy	A subject who becomes pregnant must be withdrawn from the study.	A subject who becomes pregnant must be withdrawn from study treatment (if applicable) and will not be eligible for retreatment while pregnant, but may remain in the study for observational purposes and may be considered for retreatment, if eligible, when no longer pregnant or breastfeeding.
Section 17.2.3 Time to Reduction of Response (TRR) Population		*The following text has been added:* TRR will be evaluated separately for subjects who had a 1-level and 2-level composite improvement in CR-PCSS and PR-PCSS during studies EN3835-302/303 in each buttock.
Section 17.4 Demographic and Other Baseline Characteristics	*The following text has been deleted:* These data will be transferred from EN3835-302 and EN3835-303 and will pre-populate the relevant fields of the database for this open-label study.	

2.3. Amendment 1

EN3835-304 protocol amendment 1 and amended informed consent forms (as necessary) have been reviewed and approved by the governing Institutional Review Boards (IRBs) before implementation of the amendment at each study center.

Amendment 1 was incorporated into the protocol on April 19, 2018. The major reasons for this amendment were the need to revise the eligibility criteria and the need to revise the timing for retreatment of Category I and eligible Category II subjects (ie, 1-level and 2-level responders at Day 71 of the double-blind studies, respectively), adding the potential of an unscheduled visit, conducting additional cellulite assessments, and eliminating reclassification of subjects.

Section	Original Text	Revised Text
Title Page	EN3835-304: A Phase 3b, Open-label, Long-term Study to Evaluate the Safety and Durability of Response of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy	EN3835-304: A Phase 3b, Open-label, Long-term Study to Evaluate the Safety and Temporal Pattern of Response of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy
Section 3 Sponsor Contact Information, Clinical Development Lead	[redacted], Clinical Development Office: Cell: Email:	[redacted], Clinical Development Office: Cell: Email:
Section 3 Sponsor Contact Information, Medical Monitor	[redacted] Office: Cell: Email:	[redacted] Clinical Development Office: Cell: Email:
Section 4 Synopsis, Title of Study	A Phase 3b, Open-Label, Long-Term Study To Evaluate The Safety And Durability of Response of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy	A Phase 3b, Open-label, Long-Term Study to Evaluate the Safety and Temporal Pattern of Response of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy
Section 4 Synopsis, Study Period	Estimated date last subject completed: October-2023 (est)	Estimated date last subject completed: October-2023
Section 4 Synopsis, Objective	To assess the safety, long-term immunogenicity profile, and durability of response of EN3835 in the treatment of edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, in adult women	To assess the safety, long-term immunogenicity profile, and TRR of EN3835 in the treatment of edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, in adult women
Section 4 Synopsis, Study Design	This study is a Phase 3b rollover, long-term study to assess the safety and duration of efficacy of EN3835 in the treatment of EFP. To be eligible, a subject must have participated in and completed the previous Phase 3 cellulite study EN3835-302 or EN3835-303. Subjects will be screened for study eligibility during the Day 71 Visit of their respective double-blind trial and will be offered enrollment into the trial for continued durability of response and/or safety for a period of up to 5 years.	This study is a Phase 3b rollover, long-term study to assess the safety and TRR of EN3835 in the treatment of EFP. To be eligible, a subject must have participated in and completed the previous Phase 3 cellulite study EN3835-302 or EN3835-303. Subjects will be screened for study eligibility during the Day 71 Visit of the respective double-blind trial in which the subject participated. Subjects will be offered enrollment into this trial to observe and record continued evaluation of response to

Section	Original Text	Revised Text
	Following unblinding of the double-blind studies, subjects who received placebo during the double-blind study will be discontinued, and subjects who received active EN3835 will be stratified into 3 categories:	EN3835 and/or safety for a period of up to 5 years after their initial injection in the double-blind study EN3835-302 or EN3835-303. Following unblinding of the double-blind studies, subjects who received placebo during the double-blind study will be discontinued, and subjects who received active EN3835 will be classified into one of three categories:
	Category I: 1-level Composite Responders	Category I: 1-Level Composite Responders
	Category I subjects will be eligible for one additional retreatment course in up to two buttocks in the current open-label study, beginning on Day 360 (ie, approximately 1 year after Day 71 of the double-blind studies).	Category I subjects will be eligible for one additional retreatment course in up to two buttocks concurrently in this open-label study, retreatment can begin after assessments on Day 180 (ie, approximately 6 months after Day 71 of the double-blind studies) and after unblinding of the double-blind studies confirms the subject received active EN3835. Operationally, eligible subjects who qualify for Category I status but choose NOT to receive additional retreatment will be followed with observational assessments.
	Category II will include subjects who showed an improvement in cellulite severity of at least two levels in at least one buttock in both the PR-PCSS and the CR-PCSS (ie, 2-level composite responder) in EN3835-302 or EN3835-303. These subjects will be observed for continued durability of response (defined below) approximately every 6 months, and will be observed for safety annually for up to 5 years (Day 1800). Category II subjects will not be eligible for retreatment. In the event a Category II subject shows a composite loss of efficacy back to baseline severity levels observed prior to treatment in the double-blind study, they will be re-categorized as Category III for continued safety assessments.	Category II will include subjects who showed an improvement in cellulite severity of at least two levels in at least one buttock in both the PR-PCSS and the CR-PCSS (ie, 2-level composite responder) in EN3835-302 or EN3835-303. These subjects will be observed for continued response to EN3835 and safety approximately every 6 months during the first two years and thereafter annually for up to 5 years (Day 1800). In the event a Category II subject shows a composite loss of efficacy of 1-level (ie, reduction of response by 1-level in the PR-PCSS and 1-level in the CR-PCSS compared to Day 71 ratings in the double-blind study), they will be offered retreatment. Operationally, Category II subjects who show a 1-level composite reduction in CR-PCSS and PR-PCSS, but chose NOT to receive additional retreatment, will be followed for observational assessments.
	Subjects will be assessed for safety on each day of injection during retreatment, and at 71 days after initiation of retreatment, and assessed for cellulite severity 22, 43, and 71 days following initiation of retreatment.	Subjects will be assessed for safety on each day of injection during retreatment, and at Treatment Visit 4 (Day 71) and assessed for cellulite severity on Treatment Visits 1, 2, 3, and 4 (Treatment Phase Days 1, 22, 43, and 71). Subjects will be offered one and only one retreatment course in up to 2 eligible buttocks concurrently during this 5-year long-term study.

Section	Original Text	Revised Text
	Operationally, eligible subjects who qualify for Category I status but choose NOT to receive additional retreatment will be followed as Category III subjects, with annual safety assessments.	Deleted
	Category III subjects will include all other subjects who received active EN3835 in study EN3835-302 or EN3835-303 but did not meet criteria to be included in Category I or II (ie, non-composite responders) at the time of categorical assignment. These subjects will be observed annually for safety for up to 5 years (Day 1800), and will not be eligible for retreatment during the study. As noted above, Category III will also include any subjects originally designated as Category II, but show a composite loss of efficacy back to baseline levels during the course of the study.	Category III subjects will include all other subjects who received active EN3835 in study EN3835-302 or EN3835-303 but did not meet criteria to be included in Category I or II (ie, non-composite responders) at the time of categorical assignment. These subjects will be observed for safety every 6 months for two years and then annually for up to 5 years (Day 1800), and will not be eligible for retreatment during the study.
	For study purposes, durability of response will be assessed as the continuation of at least a 2-level composite improvement in cellulite severity compared to the baseline level established during the double-blind study as assessed by both the PR-PCSS and the CR-PCSS until loss of response. Loss of response is defined as a composite worsening of cellulite severity back to baseline levels (on both the PR-PCSS and CR-PCSS), and confirmation of loss of response will be established during a follow-up visit ~2 weeks after the loss of response is first detected. The duration of response for composite 1-level responders (ie, Category I) will also be assessed at 180 days after the Day 71 Visit of the double-blind study.	For study purposes, reduction of response is defined as a composite worsening of cellulite severity improvement, and confirmation of reduction of response will be established during a follow-up visit (Durability Confirmation Visit) ~2 weeks after the reduction of response is first detected. TRR is defined as the time from assessing efficacy (Day 71 of double-blind study) to the study visit at which a composite 1-level loss of response in both PR-PCSS and CR-PCSS is observed. Durability of response is defined as a complete loss of response in which cellulite severity returns back to baseline levels (on both the PR-PCSS and CR-PCSS).
Section 4 Synopsis, Number of Subjects (Planned)	Up to approximately 420	Up to approximately 420 active subjects
Section 4 Synopsis, Diagnosis and Inclusion/ Exclusion Criteria, All Subjects (Through Day 180): Inclusion Criteria	2. Have participated in and completed the double-blind Phase 3 study EN3835-302 or EN3835 303	2. Have participated in and completed the double-blind Phase 3 study EN3835-302 or EN3835-303 (ie, assessed safety and obtained PR-PCSS and CR-PCSS ratings at Day 71/EOS of the double-blind study; does not include early termination subjects).
	3. Be willing to apply sunscreen to any treated area before each exposure to the sun while participating in the study during this period	3. Be willing to apply sunscreen to both buttocks before each exposure to the sun while participating in the study during this period

Section	Original Text	Revised Text
	4. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening	4. Be judged to be in good health, based upon the results of a physical examination, and laboratory profile at Screening
Section 4 Synopsis, Diagnosis and Inclusion/ Exclusion Criteria, All Subjects (Through Day 180): Exclusion Criteria	1. Intends to or has used any of the following for the treatment of EFP on a buttock at any time during the course of the study, including (but not limited to):	1. Intends to or has used any of the following for the treatment of EFP on a buttock at any time during the time period from Day 71 of double-blind study EN3835-302 or EN3835-303 through Day 180 Visit in study EN3835-304 (approximately 6 months after Day 71 of study EN3835-302 or EN3835-303, including (but not limited to):
	a. Liposuction in a buttock during the 12-month period before injection of study drug	a. Liposuction in a buttock
	b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock during the 12-month period before injection of study drug	b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock
	c. Any investigational treatment for EFP on a buttock during the 12-month period before injection of study drug	c. Any investigational treatment for EFP on a buttock, other than the treatment received in study EN3835-302/303
	d. Endermologie™ or similar treatments within a buttock during the 6-month period before injection of study drug	d. Endermologie™ or similar treatments within a buttock
	e. Massage therapy within a buttock during the 3-month period before injection of study drug	e. Massage therapy within a buttock
	f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before injection of study drug	f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock
	3. Has received an investigational drug or treatment within 30 days before injection of study drug	3. Has received or intends to receive an investigational drug or treatment, other than the treatment received in study EN3835-302/303 during this period
	NOTE: After unblinding of EN3835-302/ 303, subjects who received EN3835 in EN3835-302 or EN3835-303 will be placed into one of 3 categories based on their responder status. For each category, the following Inclusion and Exclusion Criteria apply beyond Day 180:	NOTE: After Day 180 Visit assessments are completed in study EN3835-304 and unblinding of EN3835-302/303, subjects who received EN3835 in EN3835-302 or EN3835-303 will be placed into one of three categories based on their responder status of each of their buttocks at Day 71 in study EN3835-302 or EN3835-303. Investigators, subjects and all site personnel will be blinded to the treatment that the subjects received in the double-blind studies until assessments at the Day 180 visit of study EN3835-304 are completed; even if this visit occurs after the EN3835-302/303 studies are unblinded by

Section	Original Text	Revised Text
		Endo. Investigator, subjects and site personnel will be unblinded on Day 180 of study EN3835-304 after Day 180 assessments are completed or at an Unscheduled Visit, pending when database lock and unblinding of studies EN3835-302/ 303 occurs relative to Day 180 of this current study EN3835-304. For each category, the following Inclusion and Exclusion Criteria apply beyond the day that the investigator, subject, and site personnel are unblinded:
Section 4 Synopsis, Diagnosis and Inclusion/ Exclusion Criteria, Category I Subjects: Inclusion Criteria	2. Maximum composite response in either or both buttocks in double-blind study EN3835-302 or EN3835-303 was ONLY a 1-level improvement on CR-PCSS/ PR-PCSS	2. Maximum composite response at Day 71 in either or both buttocks in double-blind study EN3835-302 or EN3835-303 was ONLY a 1-level improvement on CR-PCSS/PR-PCSS
	3. Prior to retreatment, at least one buttock having: a. a score of ≥2 (mild) as reported by the subject (PR-PCSS) and b. a score of ≥2 (mild) as reported by the Investigator (CR-PCSS)	Deleted
	4. Be willing to apply sunscreen to the buttocks before each exposure to the sun while participating in the retreatment portion of the study (ie, Visit 2 through Visit 6)	3. Be willing to apply sunscreen to the buttocks before each exposure to the sun while participating in the retreatment portion of the study (ie, Treatment Visit 1 through Treatment Visit 4)
	5. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening	4. Be judged to be in good health, based upon the results of a physical examination, and laboratory profile at Screening
Section 4 Synopsis, Diagnosis and Inclusion/ Exclusion Criteria, Category I Subjects: Exclusion Criteria	Added	Exclusion Criteria for Subjects Whom opt for Observations Only (ie, no retreatment): None
	A Category I subjects will not receive additional treatments and will be re-categorized to Category III status if she: 1. Is unwilling to receive one additional course of open-label retreatment (3 treatment visits) for EFP with EN3385 2. Has any of the following systemic conditions: a. Coagulation disorder b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there has been no recurrence in at least 5 years c. History of keloidal scarring or abnormal wound healing	Deleted

Section	Original Text	Revised Text
	d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases should be discussed with the Medical Monitor e. Evidence of clinically significant abnormalities on physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory values 3. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Severe skin laxity, flaccidity, and/or sagging e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer f. Has a tattoo and/or a mole located within 2 cm of the site of injection 4. Requires the following concomitant medications before or during participation in retreatment portion the trial: a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug 5. Has used any of the following for the treatment of EFP on a buttock within the timelines identified below or intends to use any of the following at any time during the course of the study: a. Liposuction in a buttock since completion of the double-blind study b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock since completion of the double-blind study c. Any investigational treatment for EFP on a buttock since completion of the double-blind study d. Endermologie™ or similar treatments within a buttock since completion of the double-blind study	

Section	Original Text	Revised Text
	e. Massage therapy within a buttock during the 3-month period before retreatment with study drug f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before retreatment with study drug 6. Prior to and during the course of retreatment (Visit 2 through Visit 6), is presently nursing or providing breast milk 7. Prior to and during the course of retreatment (Visit 2 through Visit 6), intends to become pregnant during the study 8. Prior to and during the course of retreatment (Visit 2 through Visit 6), intends to use tanning spray or tanning booths during the study 9. Has received an investigational drug or treatment within 30 days before retreatment with study drug 10. Has a known systemic allergy to collagenase or any other excipient of study drug 11. Has received any collagenase treatments at any time since completion of the double-blind study 12. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for Category I retreatment	
Section 4 Synopsis, Diagnosis and Inclusion/ Exclusion Criteria, Category II Subjects: Inclusion Criteria	2. Maximum composite response in either or both buttocks in double-blind study EN3835-302 or EN3835-303 was at least a 2-level composite improvement on CR-PCSS/PR-PCSS	2. Maximum composite response at Day 71 in either or both buttocks in double-blind study EN3835-302 or EN3835-303 was at least a 2-level composite improvement on CR-PCSS/PR-PCSS
Section 4 Synopsis, Diagnosis and Inclusion/ Exclusion Criteria, Category II Subjects: Exclusion Criteria	Added	Exclusion Criteria for Subjects Whom opt for Observation Only (ie, no retreatment):
	1. Intends to or has used any of the following for the treatment of EFP on a buttock at any time during the course of the study:	1. Intends to or has used any of the following for the treatment of EFP on a buttock at any time during the course of the study:
	a. Liposuction in a buttock during the 12-month period before injection of study drug	a. Liposuction in a buttock
	b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a	b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock

Section	Original Text	Revised Text
	buttock during the 12-month period before injection of study drug	
	c. Any investigational treatment for EFP on a buttock during the 12-month period before injection of study drug	c. Any investigational drug or treatment for EFP on a buttock (other than treatment in study EN3835-302/303)
	d. Endermologie™ or similar treatments within a buttock during the 6-month period before injection of study drug	d. Endermologie™ or similar treatments within a buttock
	e. Massage therapy within a buttock during the 3-month period before injection of study drug	e. Massage therapy within a buttock during the 3-month period before observational visit
	f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before injection of study drug	f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before observational visit
	2. Has received an investigational drug or treatment within 30 days before injection of study drug	2. Has received an investigational drug or treatment (other than treatment in study EN3835-302/303)
	3. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study	3. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study
Section 4 Synopsis, Diagnosis and Inclusion/ Exclusion Criteria, Retreatment Subjects (Eligible Subjects Whom opt to Receive Retreatment): Inclusion Criteria	Added	Retreatment Subjects (Eligible Subjects Whom opt to Receive Retreatment): **Inclusion Criteria**: 1. Voluntarily sign and date an informed consent agreement 2. Subjects who opt for retreatment must meet one of the following criterion: a. All criteria for Category I subjects; OR b. All criteria for Category II subjects, AND must have at least one buttock that at Day 71 in double-blind study EN3835-302 or EN3835-303 was at least a 2-level composite improvement on CR-PCSS/PR-PCSS that at a subsequent visit showed at least a 1-level composite reduction of response (ie, a reduction in severity by 1-level in both the PR-PCSS and CR-PCSS) compared to the Day 71 ratings in double-blind study EN3835-302/303 in that buttock(s).
Section 4 Synopsis, Diagnosis and Inclusion/ Exclusion Criteria, Retreatment Subjects (Eligible Subjects Whom opt to Receive Retreatment): Exclusion Criteria	Added	Retreatment Subjects (Eligible Subjects Whom opt to Receive Retreatment): **Exclusion Criteria**: 1. Has any of the following systemic conditions: a. Coagulation disorder b. Evidence or history of malignancy (other than excised basal-cell or squamous-cell carcinoma) unless there has been no recurrence in at least 5 years c. History of keloidal scarring or abnormal wound healing

Section	Original Text	Revised Text
		d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases should be discussed with the Medical Monitor e. Evidence of clinically significant abnormalities on physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory values
		2. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Severe skin laxity, flaccidity, and/or sagging e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer f. Has a tattoo and/or a mole located within 2 cm of the site of injection 3. Requires the following concomitant medications before or during participation in retreatment portion the trial: a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before or 7 days after injection of study drug 4. Has used any of the following for the treatment of EFP on a buttock within the timelines identified below or intends to use any of the following at any time during the course of the study: a. Liposuction in a buttock since completion of the double-blind study b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock since completion of the double-blind study c. Any investigational treatment for EFP on a buttock since completion of the double-blind study d. Endermologie™ or similar treatments within a buttock since completion of the double-blind study

Section	Original Text	Revised Text
		e. Massage therapy within a buttock during the 3-month period before retreatment with study drug f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before retreatment with study drug 5. Prior to and during the course of retreatment (Treatment Visit 1 through Treatment Visit 4), is nursing or providing breast milk 6. Prior to and during the course of retreatment (Treatment Visit 1 through Treatment Visit 4), intends to become pregnant during the study 7. Prior to and during the course of retreatment (Treatment Visit 1 through Treatment Visit 4), intends to use tanning spray or tanning booths during the study 8. Has received an investigational drug or treatment, other than treatment in study EN-3835-302/303, within 30 days before retreatment with study drug 9. Has a known systemic allergy to collagenase or any other excipient of study drug 10. Has received any collagenase treatments at any time since completion of the double-blind study 11. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for retreatment
Section 4 Synopsis, Investigational Product, Dosage and Mode of Administration	EN3835, up to 1.68 mg, subcutaneous. A dose of 0.84 mg of EN3835 per buttock will be administered as 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection) in each qualifying buttock, for a total dose of up to 1.68 mg and a total volume of up to 7.2 mL (3.6 mL per buttock). Total number of injections will be up to 24 injections per treatment visit in up to two buttocks (ie, up to 12 injections per buttock). For subjects that qualify for retreatment, there will be 3 treatment visits at 21 days intervals, beginning 1 year after initial exposure to EN3835 in their respective double-blind study (EN3835-302/303).	EN3835, up to 1.68 mg, subcutaneous. A dose of 0.84 mg of EN3835 per buttock will be administered as 12 subcutaneous injections (0.3-mL injections administered as three 0.1-mL aliquots per injection) in each qualifying buttock, for a total dose of up to 1.68 mg and a total volume of up to 7.2 mL (3.6 mL per buttock). Total number of injections will be up to 24 injections per treatment visit in up to two buttocks (ie, 12 injections per buttock). For subjects that qualify for retreatment, there will be 3 treatment visits at 21 day intervals, beginning 6 months after Day 71in their respective double-blind study (EN3835-302/303).
Section 4 Synopsis, Duration of Study	For subjects rolling over from EN3835-302/303: Up to sixty (60) months from first exposure to EN3835 in study EN3835-302/303. Screening Phase: Up to 14 days	For subjects rolling over from EN3835-302/303: Up to sixty (60) months from Day 71 (approximately 28 days after their last exposure to EN3835) of the study EN3835-302/303.

Section	Original Text	Revised Text
		Screening Phase: Up to 14 days
	Observational Phase: Subjects completing double-blind studies EN3835-302 or EN3835-303 will be assessed at visits that occur approximately every 6 months following their last visit in the double-blind study. Following unblinding of studies EN3835-302/EN3835-303, subjects who received placebo will be discontinued after Day 180. The durability of response in subjects with a ≥1-level composite PR-PCSS/CR-PCSS improvement will be assessed at 180 days, however durability of response beyond Day 180 will be assessed in subjects that received active EN3835 in one of the double-blind studies and showed at least a 2-level composite PR-PCSS/ CR-PCSS improvement (ie, reduction) in cellulite severity. All subjects who received active EN3835 in the double-blind study will be assessed for safety for up to 5 years (1800 days).	Observational Phase: Subjects completing double-blind studies EN3835-302 or EN3835-303 will be assessed at visits that occur approximately every 6 months for two years and thereafter annually for up to 5 years following their last visit in the double-blind study. Following unblinding of studies EN3835-302/EN3835-303 and after Day 180 assessments have been completed in study EN3835-304, subjects who received placebo will be discontinued. The TRR in subjects with a ≥1-level composite PR-PCSS/CR-PCSS improvement will be assessed at Day 180 in study EN3835-304, however TRR beyond Day 180 will be assessed in subjects that received active EN3835 in one of the double-blind studies or in the open-label study EN3835-304 and showed at least a 1-level composite PR-PCSS/CR-PCSS improvement (ie, reduction) in cellulite severity. All subjects who received active EN3835 in the double-blind study will be assessed for safety for up to 5 years (1800-days) after Day 71 of the double-blind studies (EN3835-302 or EN3835-303).
Section 4 Synopsis, Criteria for Evaluation	PR-CIS: a subject reported scale to assesses the visual and emotional impact of cellulite (happy, bothered, self-conscience, embarrassed, looking older or looking overweight or out of shape) using a 6-question survey, with each question rated from 0 (not at all) to 10 (extremely). A PR-CIS total score and an abbreviated PR-CIS score (excluding question 5) will be derived from these 6 individual questions.	PR-CIS: Patient Reported Cellulite Impact Scale to assess the visual and emotional impact of cellulite (happy, bothered, self-conscious, embarrassed, looking older or looking overweight or out of shape) using a 6-question survey, with each question rated from 0 (not at all) to 10 (extremely). A PR-CIS total score and an abbreviated PR-CIS score (excluding question 5) will be derived from these 6 individual questions.
	Added text	Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse)
	Subject Satisfaction with Cellulite Treatment Assessment: 5-level scale ranging from 2 (very satisfied) to −2 (very dissatisfied) for both the target and non-target buttocks	Subject Satisfaction with Cellulite Treatment Assessment: 5-level scale ranging from 2 (very satisfied) to −2 (very dissatisfied)
Section 4 Synopsis, Criteria for Evaluation	*Durability of 2-Level Composite Response*: • For the purposes of this study, treatment of EFP with EN3835 is considered 2-level composite responder once subjects show an improvement of at least 2 levels on each assessment scale (CR-PCSS/PR-PCSS) at the same visit during the double-blind study at or before Day 71 in either or both buttocks. The duration of response is	*Time to Reduce a 2-Level Composite Response*: • For the purposes of this study, a subject treated with EN3835 is considered a 2-level composite responder once an improvement of at least 2 levels on each assessment scale (PR-PCSS/CR-PCSS) is shown at the same visit during the double-blind study at or before Day 71 in either or both buttocks. The

Section	Original Text	Revised Text
	considered to *end* once a subject's cellulite severity returns to baseline on both the CR-PCSS and PR-PCSS. All cellulite assessments will be done by treated areas. Each treatment area (eg, left/right buttock) will be evaluated separately.	time until a reduction of response has occurred is considered to *end* once a subject's cellulite severity improvement reduces a composite 1-level, ie, a reduction in severity by 1-level in both the PR-PCSS and CR-PCSS. Cellulite assessments of PR-PCSS, CR-PCSS, and S-GAIS will be performed on each buttock. Each buttock will be evaluated separately. Cellulite assessment of PR-CIS, Subject satisfaction with cellulite treatment assessment, and SSRS will be performed on both buttocks.
Section 4 Synopsis, Criteria for Evaluation: Safety	• Adverse events (AEs) (including those of special interest (AESI); which are adverse events such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis; and local adverse events associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration) • Clinical laboratory tests (at retreatment visits and 28 days after last dose)	• Adverse events (AEs) (including those of special interest (AESI); which are adverse events such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, and/or any hypersensitivity reactions, including anaphylaxis; and local adverse events associated with the injection site, including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, peau d'orange changes) cutaneous adverse events • Clinical laboratory tests (prior to retreatment visits and 28 days after last retreatment dose)
Section 4 Synopsis, Statistical Methods: Analysis Population	For subjects entering open-label study period, subjects who received active EN3835 in their double-blind studies (EN3835-302/ 303) will be classified into 3 categories: Category I: 1-level Composite Responders Category II: 2-Level Composite Responders Category III: Non-Composite Responders Based on subject category, two (2) populations are considered in the statistical analysis of the study: overall safety population and durability population.	For subjects entering the open-label study period, subjects who received active EN3835 in the double-blind studies (EN3835-302/ 303) will be classified into 3 categories: Category I: 1-Level Composite Responders Category II: 2-Level Composite Responders Category III: Non-Composite Responders Based on subject category, two (2) populations are considered in the statistical analysis of the study: overall safety population and TRR population.
Section 4 Synopsis, Statistical Methods: Overall Safety Population	The overall safety population is defined as all rollover subjects who enter the open-label study period. This population will include all Category I, II, and III subjects. In addition, the safety data will be summarized by treatment period for those re-treated subjects with EN3835.	The overall safety population is defined as all subjects who enter the open-label study period and received EN3835 in study EN3835-302 or EN3835-303. This population will include all Category I, II, and III subjects. All safety analyses will be based on this population.
Section 4 Synopsis, Statistical Methods: Day-180 Observational Population	Added	*Day-180 Observational Population:* The Day-180 observational population will include all rollover subjects from studies EN3835-302/303. The safety analysis for the data obtained from Screening to Day 180 will be based on this population.

Section	Original Text	Revised Text
Section 4 Synopsis, Statistical Methods: Time to Reduction-in Response Population	*Durability Population*: The durability population is defined as all subjects who have at least 1-level/2-level improvement in both CR-PCSS and PR-PCSS score/rating during the double-blind study for either/both treated buttocks. This population will include Category I and II subjects. The durability data will be collected up to 6 months for Category I subjects and up to 5 years for Category I and II subjects.	*Time to Reduction in Response Population*: The time to reduction in response (TRR) population is defined as all subjects who have at least 1-level/2-level improvement in both CR-PCSS and PR-PCSS ratings during the double-blind study for either/both treated buttocks. This population will include Category I and II subjects. The TRR data will be collected up to 6 months for Category I subjects and up to 5 years for Category I and II subjects.
Section 4 Synopsis, ANALYSES:	The analyses of cellulite assessments will be based on durability population. The durability of response will be defined from the time of assessing the efficacy (Day 71) to the loss of response study visit.	The analyses of cellulite assessments will be based on the TRR population. The TRR will be defined from the time of assessing the efficacy (Day 71) in the double-blind study (EN3835-302/303) until the study visit in study EN3835-304 at which a composite 1-level loss of response in both PR-PCSS and CR-PCSS is observed.
	The defined endpoints will include:	The defined endpoints will include:
	• Proportion of subjects who lose their Reponses	• Proportion of subjects with reduction of response
	- Proportion of subjects that both CR-PCSS and PR-PCSS scores/ratings are back to their baseline or worse	- Proportion of subjects with both CR-PCSS and PR-PCSS ratings worsening 1-level compared to their corresponding score at Day 71 in the double-blind study (EN3835-302/303)
		- Proportion of subjects with both CR-PCSS and PR-PCSS ratings back to their baseline or worse
	- Proportion of subjects that both CR-PCSS and PR-PCSS scores/ratings are worsening 2-levels comparing to their corresponding score at Day 71 in the double-blind studies (EN3835-302/303)	- Proportion of subjects with both CR-PCSS and PR-PCSS ratings worsening 2-levels compared to their corresponding score at Day 71 in the double-blind study (EN3835-302/303)
	- Proportion of subjects that either CR-PCSS or PR-PCSS scores/ratings are worsening 2-levels comparing to their corresponding score at Day 71 in the double-blind studies (EN3835-302/303)	- Proportion of subjects with either CR-PCSS or PR-PCSS ratings worsening 2-levels compared to their corresponding score at Day 71 in the double-blind study (EN3835-302/303)
	- Proportion of subjects that both CR-PCSS and PR-PCSS scores/ratings are worsening 1-level comparing to their corresponding score at Day 71 in the double-blind studies (EN3835-302/303)	Moved to top of this bullet list
	• Changes in the PR-CIS total scores from baseline	•Changes in the PR-CIS total scores from baseline
		•Proportion of subjects at each level of improvement in the S-GAIS
	•Proportion of subjects at each level of improvement in the subject self-rating scale	•Proportion of subjects at each level of improvement in the SSRS

Section	Original Text	Revised Text
	All results for each endpoint based on the collection time points as schedule at Section 5.1, Section 5.2, and Section 5.3 will be derived and be summarized by treated area , subject category, and study visit (day) using appropriate descriptive statistics. The baseline or reference data point will be detailed in the SAP. In addition, local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration, will be recorded and evaluated for seriousness and severity (see as appropriate, Section 14.1.1, Adverse Events or Section 14.1.2, Serious Adverse Events).	All results for each endpoint based on the collection time points will be derived and be summarized by treated area, treatment exposure category, and study visit (day) using descriptive statistics. In addition, local AEs associated with the injection site, including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, peau d'orange changes) cutaneous adverse events will be recorded and evaluated for seriousness and severity.
Section 4 Synopsis, ANAYLSES: Immunogenicity	Anti-AUX-I and anti-AUX-II antibody levels and a subset of neutralizing Anti-AUX-I and anti-AUX-II antibody will be summarized using appropriate descriptive statistics.	Anti-AUX-I and anti-AUX-II antibody levels and a subset of subjects' samples anti-AUX-I and anti-AUX-II neutralizing antibodies will be summarized using descriptive statistics.
Section 5.1 Schedule of Events, Up to 180 Days	Column crossing all rows stating (EN3835-302/303 Study Unblind)	Deleted
	Column heading: Screening (≥Day 71 Visit of Double-blind Study)(±14 days)	Column heading: Screening (≥Day 71 Visit[a] of Double-blind Study)(±14 days)
	Column heading: Visit 1 Day 180 (±14 d)	Column heading: Visit 1 Day 180[b] (±14 days) M6
	Added	Column: Durability Confirmation Visit [l] Digital Photography: X Review assessments' training and use materials: X Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS): X [f,g] Review assessment's training and use materials: X Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS): X [h] Local Safety assessments: X [k] Adverse Events: Monitored throughout study
	Added	Column: Unscheduled Clinic Visit [c] Digital Photography: X Prior/concomitant medications/procedures [a]: X Body weight: X Vital signs: X Clinical Laboratory: X Pregnancy testing [b]: X Unblinding of Investigator, subject and site to subjects' treatments in EN3835-302/303: X [i] Assignment of Subject to Category I, II, or III: X [j]

Section	Original Text	Revised Text
		Local Safety assessments: X [k] Adverse Events: Monitored throughout study
	Informed consent: Screening: X	Informed consent [m] Screening: X; Day 180 Visit: X
	Medical history including previous EFP treatments; and associated Visit X's	Deleted row
	Added row	Review assessments' training and use materials, Screening: X; Visit 1 Day 180: X
	Added row	Subject Global Aesthetic Improvement (S-GAIS) , Screening: X [d]; Visit 1 Day 180: X [d]
	Subject Self Reporting Scale	Subject Self-Rating Scale
	Added row	Review assessment's training and use materials, Screening: X; Visit 1 Day 180: X
	Added row	Local Safety assessments: Screening: X[k]; Visit 1 Day 180: X [k]; Unscheduled Clinic Visit: X [k]
	Adverse Events: X	Adverse events: Monitored throughout study
	[a] Including Xiaflex	[d] Including XIAFLEX as a possible concomitant medications; the use of the word 'prior' refers to the period between the last visit from the previous Phase 3 clinical study through the signing of informed consent in the EN3835-304 study.
	[b] Serum pregnancy test occurs on Screening visit (carried over from Day 71/EOS visit of EN3835-302/303); Urine pregnancy test on Day 180 Visit	[e] Serum pregnancy test occurs on Screening visit (carried over from Day 71/EOS visit of EN3835-302/303); urine pregnancy test on Day 180 Visit and, if deemed necessary, at an Unscheduled Visit.
	Added	[b] Visit 1 Day 180 is in study EN3835-304; approximately 180 days after Day 71 of double-blind study.
		[c] During unscheduled visits, the Investigator or designee may perform any study procedure that they deem clinically necessary (eg, vital signs, clinical lab assessments, and pregnancy test).
		[i] Depending on the date of unblinding of subject's treatment in EN3835-302/303; investigators, subjects, and site personnel may be unblinded at Day 180 Visit after assessments are completed or at a time thereafter during an unscheduled visit. If database lock occurs prior to Day 180, the investigator, subjects, and site personnel will remained blinded until Day 180 Visit assessments are completed.
		[j] Assignment of subjects to Categories will occur after unblinding of investigators, subject and site personnel to subjects' treatment in EN3835-302/303 and will

Section	Original Text	Revised Text
		depend on treatment and Day 71 cellulite severity improvements. Depending on the date of the database lock of the double-blind studies, assignments may occur at Day 180 Visit after assessments are completed or at a time thereafter during an unscheduled visit.
		[k] Local adverse events associated with the injection site, including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, peau d'orange changes) cutaneous adverse events, will be recorded and evaluated for seriousness and severity
		[l] If the composite (CR-PCSS and PR-PCSS) ratings worsen by at least 1-level composite response ratings at Day 180 Visit for a subject that had a 2-level composite improvement at Day 71 of the double-blind study, an additional visit should be scheduled 14 days (± 5 days) later to confirm reduction of response, via re-assessment with the CR-PCSS and PR-PCSS.
		[m] Informed consent at Screening will address activities up through Day 180 Visit. Informed consent at Day 180 Visit will address the classification of subjects into Categories I, II, and III and activities and assessments that they will undergo.
	d=Days; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of Study	EFP=Edematous fibrosclerotic panniculopathy; EOS=End of Study; M=Month
Section 5.2 Schedule of Events, Eligible Category I/II Subjects – Treatment Session Assessments	5.2 Category I Subjects	5.2 Eligible Category I/II Subjects – Treatment Session Assessments
	Column headings: Procedures [a] ;Visit 2 Screen B Day 360 (±7 d); Visit 3 Day 374 (±3 d); Visit 4 Day 395 (±3 d); Visit 5 Day 416 (±3 d): Visit 6 Day 444 (±5 d); Visit 7 Day 540 (±30 d); Visit 8 Day 720 (±30 d); Visit 9 Day 1080 (±30 d), Visit 10 Day 1440 (±30 d); Visit 11 Day 1800/EOS (±30 d)	Column headings: Procedures [a]; Screening B [b] (Day -14 to -1 relative to Tx Visit 1); Tx Visit 1 Tx Session 1 Day 1; Tx Visit 2 Tx Session 2; Day 22 (±3 days); Tx Visit 3 Tx Session 3 Day 43 (±3 days); Tx Visit 4 End of Treatment/ Early Termination Day 71 (+5 days) [c]; Unscheduled Clinic Visit [a]
	Added	Column: Unscheduled Clinic Visit [c] Digital Photography: X Prior/concomitant medications/procedures [a]: X Body weight: X Vital signs: X Clinical Laboratory: X Pregnancy testing: X [j]

Section	Original Text	Revised Text
		Injection site reactions/local tolerability in the buttocks [p]: X Adverse Events: Monitored throughout study
	Informed consent: Screening B [b]: XX [q]	Informed consent: Screening B [b]: X [q]
	Medical history/EFP history including previous treatments: Screening B [b]: X	Deleted row
	Height; Visit 6 Day 444: X	Height; Screening B [b]: X
	Added row	ECG; Screening B [b]: X[i]
	Added row	Review assessments' training and use materials, Screening B [b]: X; Tx Visit 4 Day 71: X
	Added row	Subject Global Aesthetic Improvement (S-GAIS) [l], Screening B [b]: X; Tx Visit 4 Day 71: X
	Patient Reported Cellulite Impact Scale (PR-CIS) Subject Satisfaction With Cellulite Treatment Assessment Subject Self Reporting Scale (SSRS)	Subject Global Aesthetic Improvement Scale (S-GAIS) [l] Patient Reported Cellulite Impact Scale (PR-CIS) [l] Subject Satisfaction With Cellulite Treatment Assessment [l] Subject Self-Rating Scale (SSRS)
	Added row	Review assessment's training and use materials, Screening B [b]: X; Tx Visit 4 Day 71: X
	[a] During unscheduled visits, the Investigator or designee may perform any study procedure that they deem clinically necessary (eg, vital signs, clinical lab assessments, and pregnancy test).	[a] During unscheduled visits, the Investigator or designee may perform any study procedure, except study drug administration, that they deem clinically necessary (eg, vital signs, clinical lab assessments, and and/or pregnancy test).
	Added	[b] After the study drug treatment blind is broken in study EN3835-302/303 and subjects have been classified based on Day 71 composite responses in study EN3835-302/303, Category and Category II subjects that qualify for treatment may elect to receive one and only one course of EN3835 retreatment (ie, 3 treatment sessions) in up to 2 buttocks.
		[c] Upon completion of treatment, subject will be followed at intervals as in Section 5.3; if the 71-day treatment period overlaps with an Observation Visit in Section 5.3 for a subject, that particular Observation visit will be skipped and the subject will be assessed at the next scheduled Observation Visit in Section 5.3
	[d] Only includes the areas receiving retreatment	Deleted
	[e] Including Xiaflex	[f] Including XIAFLEX as a possible concomitant medication; the use of the word

Section	Original Text	Revised Text
		'prior' refers to the period between the last visit from the previous Phase 3 clinical study through the signing of informed consent in the EN3835-304 study.
	[h] Urine pregnancy test	[j] Serum pregnancy test on Screening visit and Day 71/EOS visit; urine pregnancy test on Day 1, Day 22, and Day 43 visits and Unscheduled Visit.
	[l] Each of the subject's buttocks receiving retreatment must have scores/ratings of at least 2 in both the CR-PCSS and PR-PCSS.	[o] Each buttock of Category I subjects are eligible to receive retreatment; at least one of Category II subject's buttocks must have loss a 1-level composite rating in both CR-PCSS and PR-PCSS compared to double-blind study Day 71 ratings to be eligible to receive retreatment.
	Added	[p] Local adverse events associated with the injection site, including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, peau d'orange changes) cutaneous adverse events, will be recorded and evaluated for seriousness and severity.
		[q] Informed consent for Category I and eligible Category II subjects who opt to receive retreatment.
	NOTE: Subjects who qualify for Category I status who choose NOT to receive additional retreatment will be considered Category III subjects.	Deleted
	d=Days; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study	ECG=Electrocardiogram; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study; Tx=Treatment

Section	Original Text	Revised Text
Section 5.3 Schedule of Events, Category I/II Subjects – Observation Assessments	5.3 Category II Subjects	5.3 Category I/II Subjects – Observation Assessments
	Column headings; Procedures; Visit 2 Day 360 (±30 d); Visit 3 Day 540 (±30 d); Visit 4 Day 720 (±30 d); Visit 5 Day 900 (±30 d); Visit 6 Day 1080 (±30 d); Visit 7 Day 1260 (±30 d); Visit 8 Day 1440 (±30 d); Visit 9 Day 1620 (±30 d); Visit 10 Day 1800/EOS (±30 d) Durability Confirmation Visit [a]	Column headings: Procedures; Visit 2 Day 360 (±30 d) (M12); Visit 3 Day 540 (±30 d) (M18); Visit 4 Day 720 (±30 d) (M24); Visit 5 Day 1080 (±30 d) (M36); Visit 6 Day 1440 (±30 d) (M48); Visit 7 Day 1800/EOS (±30 d) (M60); Durability Confirmation Visit [a]; Unscheduled Clinic Visit [b]
	Added	Column: Unscheduled Clinic Visit [b] Digital Photography: X Prior/concomitant medications/procedures [a]: X Local safety assessments [g]: X Adverse Events: Monitored throughout study
	Informed consent: Visit 2: X	Verification of informed consent: Visit 2: X
	Medical history/EFP history including previous treatments: Screening B [b]: X	Deleted row
	Added row	Review assessments' training and use materials, Visits 2 – 7: X
	Added row	Subject Global Aesthetic Improvement (S-GAIS) [l], Visits 2 – 7: X
	Patient Reported Cellulite Impact Scale (PR-CIS) Subject Satisfaction With Cellulite Treatment Assessment Subject Self Reporting Scale (SSRS)	Subject Global Aesthetic Improvement Scale (S-GAIS) [e] Patient Reported Cellulite Impact Scale (PR-CIS) [e] Subject Satisfaction With Cellulite Treatment Assessment [e] Subject Self-Rating Scale (SSRS)
	Added row	Review assessment's training and use materials, Visits 2 – 7: X
		Local safety assessments [g]: all Visits: Xs
	[a] If the composite (CR-PCSS and PR-PCSS) score/rating for cellulite severity goes back to baseline values for a subject, an additional visit should be scheduled 14 days later to confirm durability, via re-assessment with CR-PCSS and PR-PCSS. If loss of response is confirmed, subjects will continue with annual visits only (ie, Days 720, 1080, 1440, and 1800).	[a] If the composite (CR-PCSS and PR-PCSS) ratings worsen by at least 1 level composite response ratings for a subject, an additional visit should be scheduled 14 days later to confirm reduction of response, via re-assessment with the CR-PCSS and PR-PCSS. If reduction of response is confirmed, subjects will be offered one course of retreatment (one and only one course of retreatment in up to 2 buttocks concurrently will be offered to an individual subject during this open-label study from Visit 1 to Visit 6 (approximately 6 to 48 months after Day 71 of the double-blind study, respectively) after which they will continue with observation visits only.
	[b] Photography and assessment should be limited to the regions that show a 2-level composite improvement (ie, if only one	Deleted

Section	Original Text	Revised Text
	buttock showed a 2-level composite response, only that buttock should be photographed.	
	[e] Including Xiaflex	[c] Including XIAFLEX as a concomitant medication; the use of the word 'prior' refers to the period between the last visit from the previous Phase 3 clinical study through the signing of informed consent in the EN3835-304 study.
	Added	[b] During unscheduled visits, the Investigator or designee may perform any study procedure that they deem clinically necessary (eg, vital signs and/or clinical lab assessments).
	[f] Before injection.	Deleted
	[h] Urine pregnancy test	Deleted
	[j] Assessment made via photographs (if treatment visit, use photographs taken before marking dimples and injection sites).	[e] Assessment made via photographs.
	[k] Assessment of each re-treated buttock (independently if both buttocks received retreatment).	[f] Assessment of each of the 2 buttocks is to be made independently.
	[l] Each of the subject's buttocks receiving retreatment must have scores/ratings of at least 2 in both the CR-PCSS and PR-PCSS. NOTE: Subjects who qualify for Category I status who choose NOT to receive additional retreatment will be considered Category III subjects.	Deleted
	Added	[g] Local adverse events associated with the injection site, including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, peau d'orange changes) cutaneous adverse events, will be recorded and evaluated for seriousness and severity.
	d=Days; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study	d=Days; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study; M=Month(s)
Section 5.4 Schedule of Events, Category III Subjects - Assessments	5.4 Category III Subjects	5.4 Category III Subject Assessments
	Column headings: Procedures; Visit 2 Day 360 (±30 d); Visit 3 Day 720 (±30 d); Visit 4 Day 1080 (±30 d); Visit 5 Day 1440 (±30 d); Visit 6 Day 1800/EOS (±30 d)	Procedures; Visit 2 Day 360 (±30 d) (M12); Visit 3 Day 540 (±30 d) (M18); Visit 4 Day 720 (±30 d) (M24); Visit 5 Day 1080 (±30 d) (M36); Visit 6 Day 1440 (±30 d) (M48); Visit 7 Day 1800/EOS (±30 d) (M60)
	Added column	Visit 3 Day 540 (±30 d) (M18): Prior/concomitant medications/procedures [a]: X Anti-AUX-I/anti-AUX-II antibody level: X Local safety assessments [b]: X

Section	Original Text	Revised Text
		Adverse events: Monitored throughout study
	Added column	Unscheduled Clinic Visit [c] Prior/concomitant medications/procedures [a]: X Local safety assessments [b]: X Adverse events: Monitored throughout study
	Informed consent: Visit 2: X	Verification of informed consent: Visit 2: X
	Medical history including previous EFP treatments; Visit 2 Day 360: X; Visit 3 Day 720:X; Visit 4 Day 1080: X; Visit 5 Day 1440: X; Visit 6 Day 1800/EOS: X	Deleted row
	Added spacer row	Collection of samples:
	[a] Including Xiaflex	[a] Including XIAFLEX as a concomitant medication; the use of the word 'prior' refers to the period between the last visit from the previous Phase 3 clinical study through the signing of informed consent in the EN3835-304 study.
	Added	[b] Local adverse events associated with the injection site, including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, peau d'orange changes) cutaneous adverse events, will be recorded and evaluated for seriousness and severity
		[c] During unscheduled visits, the Investigator or designee may perform any study procedure that they deem clinically necessary.
	NOTE: Subjects who qualify for Category I status who choose NOT to receive additional retreatment will be considered Category III subjects	Deleted
	d=Days; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study	d=Days; EOS=End of study; M=Month
Section 7 List of Abbreviations	Added	TRR Time to reduction of response
Section 9.2 Secondary Objectives	The secondary objective of this study is to assess the durability of response of EN3835 in the treatment of edematous fibrosclerotic panniculopathy (EFP) in adult women.	The secondary objective of this study is to assess the TRR to EN3835 in the treatment of edematous fibrosclerotic panniculopathy (EFP) in adult women.

Section	Original Text	Revised Text
Section 10.1 Study Design	This open-label extension study will be performed at multiple centers currently participating in the double-blind, placebo-controlled, parent trial (EN3835-302/ EN3835-303) in the United States. Following completion of safety and cellulite assessments at Day 71 of the double-blind study (EN3835-302/303), subjects will be asked to continue in the open-label extension to the double-blind study (ie, EN3835-304, the current study). Assessments made at Day 71/EOS of the double-blind study will serve as initial screening for the current open-label extension study. At the time of entry into the open-label study, subjects and Investigators will remain blinded to study drug. Until the EN3835-302/303 study drug blind is broken by the Sponsor, subjects will undergo observation-only visits at 6 months ± 14 days, where both safety and cellulite severity assessments of the treated quadrant will be made. Upon completion and unblinding of the double-blind studies EN3835-302/303, subjects who received placebo during the double-blind studies will be discontinued, and subjects who received active EN3835 will be stratified into 3 Categories: Category I: 1-level Composite Responders Category II: 2-Level Composite Responders Category III: Non-Composite Responders Category I subjects will be eligible for one additional retreatment course in up to two buttocks in the current open-label study, beginning on Day 360. Only buttocks with a composite 1-level improvement will be retreated. Assessment of open-label efficacy will be determined for up to 71 Days following retreatment, after which subjects will be observed annually for safety for up to 5 years (Day 1800). Eligible subjects who qualify for Category I status who choose NOT to receive additional retreatment will operationally be treated as Category III subjects. Category II will include subjects who showed an improvement in cellulite severity of at least two levels in at least one buttock in both the PR-PCSS and the CR-PCSS (ie, 2-level composite responder) in EN3835-302 or EN3835-303. These subjects will be observed for continued durability of	This open-label extension study will be performed at multiple centers currently participating in the double-blind, placebo-controlled, parent trials (EN3835-302/EN3835-303) in the United States. Following completion of safety and cellulite assessments (at least PR-PCSS and CR-PCSS) at Day 71 of the double-blind study (EN3835-302/303), subjects will be asked to continue in the open-label extension to the double-blind study (ie, EN3835-304, the current study). Assessments made at Day 71/EOS of the double-blind study will serve as initial screening for the current open-label extension study. At the time of entry into the open-label study and at Visit 1 at Day 180 of study EN3835-304 (approximately 6 months after Day 71 of study EN3835-302/302, subjects and Investigators and site personnel will remain blinded to study drug treatment received in the double-blind study. Even if the EN3835-302/303 study drug blind is broken by the Sponsor; subjects, Investigators and site personnel in study EN3835-304 will remain blinded until after Day 180 safety and cellulite severity assessments of each treatment area are completed. Upon completion and unblinding of the double-blind studies EN3835-302/303 (which may occur immediately after Day 180 Visit assessments are completed if the study drug blind has been broken by Sponsor, or may occur during an visit (Unscheduled Visit) after Day 180 of the blind is not broken by Sponsor until sometime after Day 180), subjects who received placebo during the double-blind studies will be discontinued, and subjects who received active EN3835 will be classified into one of three Categories: Category I: 1-Level Composite Responders Category II: 2-Level Composite Responders Category III: Non-Composite Responders Category I subjects will be eligible for one additional retreatment course in up to two buttocks in the current open-label study. Retreatment may begin on Day 180 if the study drug blind from the double-blind study (EN3835-302/303) has been broken. Only buttocks with a composite 1-level improvement or less will be retreated. Assessment of open-label efficacy following

Section	Original Text	Revised Text
	response (defined below) approximately every 6 months, and will be observed for safety annually for up to 5 years (Day 1800). Category II subjects will not be eligible for retreatment. Category III subjects will include all other subjects who received active EN3835 in study EN3835-302 or EN3835-303 but did not meet criteria to be included in Category I or II (ie, non-composite responders). These subjects will be observed annually for safety for up to 5 years (Day 1800), and will not be eligible for retreatment during the study. The retreatment course for Category I subjects will consist of 3 treatment sessions separated by 21 days. Each retreatment session will consist of up to 12 injections (0.07 mg/0.3 mL per injection) of EN3835 for a dose of 0.84 mg and volume of 3.6 mL (identical to the treatment course administered in the double-blind study), in each qualifying buttock (Table 3). Subjects will be assessed for safety on each day of injection during retreatment, and at 71 days after initiation of retreatment, and assessed for cellulite severity 22, 43, and 71 days following initiation of retreatment. For study purposes, durability of response is defined as the duration, until loss of response, of composite improvement in cellulite severity compared to the baseline level established during the double-blind study as assessed by both the PR-PCSS and the CR-PCSS until loss of response. Loss of response is defined as a composite worsening of cellulite severity back to baseline (for Category I), or of at least two levels (ie, worsening of 2 levels on both the PR-PCSS and CR-PCSS) for Category II. For open-label assessment of durability in Category II subjects, confirmation of loss of response will be established during a follow-up visit ~2 weeks after the loss of response is first detected. Once enrolled in the current open-label study, subjects will again receive instructions for use of the PR-PCSS and will subsequently use the scale to rate the severity of their cellulite in each of the treated areas on standardized computer monitors with the PR-PCSS instrument. Both the Investigator and the subject will remain blinded to each other's assessments	retreatment will be determined up to Treatment Visit 4 (Day 71 + 5 days), after which subjects will be observed, depending when during the 5 year period the subject receives retreatment, for every 6 months for 2 years and then annually for up to 5 years (Day 1800) after Day 71 of study EN3835-302/303. Eligible subjects who qualify for Category I status who choose NOT to receive additional retreatment will have observation visits (Visits 2-7) as detailed in Section 5.3. Category II will include subjects who showed an improvement in cellulite severity of at least two levels in at least one buttock in both the PR-PCSS and the CR-PCSS (ie, 2-level composite responder) in EN3835-302 or EN3835-303. These subjects will be observed for TRR (defined below) and safety approximately every 6 months for 2 years and will be observed annually for up to 5 years (Day 1800) from Day 71 of the double-blind studies. Category II subjects who lose 1-level composite response in at least one buttock relative to the composite improvement (at least one composite level) at Day 71 of the double-blind study will be eligible for retreatment as detailed in Section 5.2; after which they will be observed at observation visits as detailed in Section 5.3. Category I and Category II subjects who in the observational phase of the study, will have cellulite assessments completed during the observational visits at Months 12, 18, 24, 36, 48, and 60. At Months 12, 18, 24, 36, and 48, if the ratings indicate that the buttock(s) is eligible for retreatments and the subject has not received EN3835 previously in study EN3835-304, the subject will be offered one course of treatment for the eligible buttock(s); one course of concurrent treatment for up to two eligible buttocks. Category III subjects will include all other subjects who received active EN3835 in study EN3835-302 or EN3835-303 but did not meet criteria to be included in Category I or II (ie, non-composite responders). These subjects will be observed for safety every 6 months for 2 years and annually for up to 5 years (Day 1800) as detailed in Section 5.4, and will not be eligible for retreatment during the study. The retreatment course for Category I subjects and for eligible Category II subjects

Section	Original Text	Revised Text
	for the duration of the open-label study, even after the blind is broken for each double-blind study by the Sponsor. The Schedule of Events for all subjects up through 180 days following studies EN3835-302/303 is provided in Section 5.1. Beyond Day 180, the Schedule of Events for Category I, II, and II subjects are provided in Section 5.2, Section 5.3, and Section 5.4, respectively.	will consist of 3 treatment sessions separated by 21 days. Each retreatment session will consist of 12 injections (0.07 mg/0.3 mL per injection) of EN3835 for a dose of 0.84 mg and volume of 3.6 mL (identical to the treatment course administered in the double-blind study), in each qualifying buttock (Table 3) in up to two buttocks treated concurrently. One and only one retreatment course in up to 2 qualifying buttocks concurrently will be offered to Category I and eligible Category II subjects during this 5 year study. After initiation of retreatment (on Treatment Visit 1; Treatment Day 1), subjects will be assessed for safety on each day of injection during retreatment, and assessed for safety and cellulite severity on Treatment Visit 2 (Day 22), Treatment Visit 3 (Day 43) and Treatment Visit 4 (Day 71). For study purposes; reduction of response (ie, lessening of response or loss of response) is defined as a 1-level composite worsening of cellulite severity improvement observed at Day 71 of the double-blind studies (EN3835-302/303) on both the PR-PCSS and CR-PCSS. TRR is defined as the time from assessing efficacy (Day 71 of double-blind study) to the study visit at which a composite 1-level loss of response in both PR-PCSS and CR-PCSS is observed. Durability of response is defined as a complete loss of response in which cellulite severity returns back to baseline levels (on both the PR-PCSS and CR-PCSS on Day 1 of the double-blind studies). Confirmation of reduction of response and/or complete loss of response will be established during a follow-up visit ~2 weeks after a composite reduction of response is first detected. Once enrolled in the current open-label study, subjects will again receive instructions for use of the PR-PCSS and will subsequently use the scale to rate the severity of their cellulite in each of the treatment areas on a standardized computer monitor with the PR-PCSS instrument. Both the Investigator and the subject will remain blinded to each other's assessments for the duration of the open-label study, even after the study drug treatment blind is broken for each double-blind study by the Sponsor. Throughout the study, subjects and Investigators will be provided training

Section	Original Text	Revised Text
		materials and will refresh on training prior to the use of each cellulite assessment at each visit. The Schedule of Events for all subjects up through 180 days following studies EN3835-302/303 is provided in Section 5.1. Beyond Day 180, the Schedule of Events for subjects classified as categories I and II and who are eligible and opt to receive retreatment is provided in Section 5.2 and in observational phase of study Section 5.3. The Schedule of Events for subjects in Category II who are not eligible for retreatment, or are in Category I and II and who are eligible but opt not to have retreatment, is provided in Section 5.3. The Schedule of Events for Category III subjects is shown in Section 5.4.
Figure 1 Study Design	[Flow chart]	[Revised flow chart]
Table 3	Study Retreatment (Category I Subjects Only) Dose (mg) at Each Treatment Visit 0.84 mg per buttock × 2 buttocks = 1.68 mg (12 injections per buttock × 0.07 mg/injection × up to 2 buttocks)	Study Retreatment (Category I Subjects and Eligible Category II Subjects Only) Dose (mg) at Each Treatment Visit 0.84 mg per buttock × up to 2 buttocks = 1.68 mg (12 injections per buttock × 0.07 mg/injection × up to 2 buttocks)
Section 10.2 Selection of Doses	The findings from previous studies that the majority of adverse events after EN3835 treatment are local to the injection site and that there is no quantifiable systemic exposure observed after concurrent treatment of two buttocks (total dose of 1.68 mg) supports the proposed study to evaluate EN3835 treatment of two buttocks	The findings from previous studies that the majority of adverse events after EN3835 treatment are local to the injection site and that there is no quantifiable systemic exposure observed after concurrent treatment of two buttocks (0.84 mg/buttock; total dose of 1.68 mg) supports the proposed dose to evaluate EN3835 in treatment of one or both buttocks.
Section 10.3 Study Drug Administration (Category I Subjects and Eligible Category II Subjects)	Study Drug Administration (Category I Subjects)	Study Drug Administration (Category I Subjects and Eligible Category II Subjects)
	Added	Position B should be towards the head (cephalad) of the subject. Position C should be towards the feet (caudal) of the subject. In most cases, the plane containing injection points A, B, and C will be parallel to the long axis of the subject's body.
	NOTE: EN3835 is a foreign protein and Investigators should be prepared to address and manage an allergic reaction should it occur. At the time of each injection, a 1:1,000 solution of epinephrine for injection, 50-mg diphenhydramine injection or a suitable equivalent, and oxygen must be	NOTE: EN3835 is a foreign protein and Investigators must be prepared to address and manage an allergic reaction should it occur. At the time of each injection, a 1:1,000 solution of epinephrine for injection, 50-mg diphenhydramine injection or a suitable equivalent, and oxygen must be available,

Section	Original Text	Revised Text
	available with the Investigator and site staff must be familiar with their use.	and the Investigator and site staff must be familiar with their use.
Section 10.5 Discussion of Study Design, Including the Choice of Control Groups	The design of this study was based on the primary objective to evaluate the safety and durability of response of EN3835 0.84 mg per buttock in the concurrent treatment (total dose of up to 1.68 mg) of 2 bilateral buttocks with EFP in adult women. The study is being conducted as a multi-center, open-label extension study. Safety data and immunogenicity after repeat exposure (retreatment) and monitoring of previously EN3835 treated subjects for up to 5 years (1800 days following Day 71 of double-blind), and Durability of the response to EN3835 (cellulite severity assessments) will be assessed at various time points.	This study is a long-term follow-up study of subjects who received EN3835 0.84 mg per buttock in the concurrent treatment (total dose of up to 1.68 mg) of 2 bilateral buttocks with EFP in adult women in a 71-day double-blind, placebo-controlled study (EN3835-302 or EN3835-303). After completion in one of the aforementioned studies, subjects will be followed for up to 5 years from the Day 71 of the double-blind study (EN3835-302/303), which is approximately 28 days after the last exposure of EN3835 in study EN3835-302/303. Study EN3835-304 is being conducted as a multi-center, open-label extension study. • Safety data, immunogenicity, and responsiveness after repeat exposure (retreatment) and monitoring of previously EN3835 treated subjects for up to 5 years (1800 days following Day 71 of double-blind), • Safety data, immunogenicity and responsiveness after repeat exposure (retreatment) in subjects that show a reduction from the improvement observed at Day 71 of the double-blind studies and • Time to reduction in the response to EN3835 using cellulite severity assessments will be evaluated at various time points.
Section 11.1.1 All Subjects (Through Day 180)	For the period prior to unblinding of EN3835-302/303, in order to be eligible to participate in the study, subjects must meet the following inclusion criteria:	In order to be eligible to participate in the study, subjects must meet the following inclusion criteria:
	2. Have participated in and completed the double-blind Phase 3 study EN3835-302 or EN3835-303	2. Have participated in and completed the double-blind Phase 3 study EN3835-302 or EN3835-303 (ie, assessed safety and obtained PR-PCSS and CR-PCSS ratings at Day 71/EOS of the double-blind study; does not include early termination subjects).
	4. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening	4. Be judged to be in good health, based upon the results of a physical examination, and laboratory profile at Screening
	NOTE: After unblinding of EN3835-302/ 303, subjects who received active EN3835 will be placed into one of 3 categories based on their responder status (Section 10.1). For each category, the following Inclusion Criteria apply beyond Day 180.	NOTE: After Day 180 Visit assessments are completed in study EN3835-304 and unblinding of EN3835-302/303, subjects who received EN3835 in EN3835-302 or EN3835-303 will be placed into one of three categories based on their responder status of each of their buttocks at Day 71 in study EN3835-302 or EN3835-303 (Section 10.1).

Section	Original Text	Revised Text
		Investigators, subjects and all site personnel will be blinded to the treatment that the subjects received in the double-blind studies until assessments at the Day 180 visit of study EN3835-304 are completed; even if this visit occurs after the EN3835-302/303 studies are unblinded by Endo. Investigator, subjects and site personnel will be unblinded on Day 180 of study EN3835-304 after Day 180 assessments are completed or at an Unscheduled Visit, pending when database lock and unblinding of studies EN3835-302/ 303 occurs relative to Day 180 of this current study EN3835-304. For each category, the following Inclusion and Exclusion Criteria apply beyond the day that the investigator, subject, and site personnel are unblinded:
Section 11.1.2 Category I Subjects (Post Unblinding of EN3835-302/303)	3. At least one buttock having: a. a score of ≥2 (mild) as reported by the subject (PR-PCSS), and b. a score of ≥2 (mild) as reported by the Investigator (CR-PCSS)	Deleted
	4. Be willing to apply sunscreen to the buttocks before each exposure to the sun while participating in the retreatment portion of the study (ie, Visit 2 through Visit 6)	3. Be willing to apply sunscreen to the buttocks before each exposure to the sun while participating in the retreatment portion of the study (ie, Treatment Visit 1 through Treatment Visit 4)
	5. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening	4. Be judged to be in good health, based upon the results of a physical examination, and laboratory profile at Screening
Section 11.1.3 Category II Subjects (Post Unblinding of EN3835-302/303)	2. Maximum composite response in either or both buttocks in double-blind study EN3835 302 or EN3835-303 was at least a 2-level composite improvement on CR PCSS/PR PCSS	2. Maximum composite response at Day 71 in either or both buttocks in double-blind study EN3835-302 or EN3835-303 was at least a 2-level composite improvement on CR-PCSS/PR-PCSS
Section 11.1.5 Retreatment Subjects (Eligible Subjects Whom opt to Receive Retreatment)	Added	1. Voluntarily sign and date an informed consent agreement 2. Subjects who opt for retreatment must meet one of the following criterion: a. All criteria for Category I subjects; OR b. All criteria for Category II subjects, AND must have at least one buttock that at Day 71 in double-blind study EN3835-302 or EN3835-303 was at least a 2-level composite improvement on CR-PCSS/ PR-PCSS that at a subsequent visit showed at least a 1-level composite reduction of response (ie, a reduction in severity by 1-level in both the PR-PCSS and CR-PCSS) compared to the Day 71 ratings in double-blind study EN3835-302/303 in that buttock(s).

Section	Original Text	Revised Text
Section 11.2.1 All Subjects (Through Day 180)	For the period prior to unblinding of EN3835-302/303, in order to be eligible to participate in the study, subjects must meet the following exclusion criteria: A subject will be excluded from study participation if she:	For the period from completing Day 71 of the double-blind study (EN3835-302 or EN3835-303) through Day 180 (Visit 1) of study EN3835-304, in order to be eligible to participate in the study, subjects must meet the following exclusion criteria: A subject will be excluded from study participation if she:
	1. Intends to or has used any of the following for the treatment of EFP on a buttock at any time during the course of the study, including (but not limited to):	1. Intends to or has used any of the following for the treatment of EFP on a buttock at any time during the time period from Day 71 of double-blind study EN3835-302 or EN3835-303 through Day 180 Visit in study EN3835-304 (approximately 6 months after Day 71 of study EN3835-302 or EN3835-303, including (but not limited to):
	a. Liposuction in a buttock during the 12-month period before injection of study drug	a. Liposuction in a buttock
	b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock during the 12-month period before injection of study drug	b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock
	c. Any investigational treatment for EFP on a buttock during the 12 month period before injection of study drug	c. Any investigational treatment for EFP on a buttock, other than the treatment received in study EN3835-302/303
	d. Endermologie™ or similar treatments within a buttock during the 6-month period before injection of study drug	d. Endermologie™ or similar treatments within a buttock
	e. Massage therapy within a buttock during the 3-month period before injection of study drug	e. Massage therapy within a buttock and/or home therapies to prevent or mitigate EFP within a buttock
	f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before injection of study drug	f. Creams (eg, Celluvera™, TriLastin®)
	2. Intends to use tanning spray or tanning booths during the study	2. Intends to use tanning spray or tanning booths during this period
	3. Has received an investigational drug or treatment within 30 days before injection of study drug	3. Has received or intends to receive an investigational drug or treatment, other than the treatment received in study EN3835-302/303 during this period
	4. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study	4. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study
	NOTE: After unblinding of EN3835-302/303, subjects who received active EN3835 will be placed into one of 3 categories based on their responder status (Section 10.1). For	NOTE: After Day 180 Visit assessments are completed in study EN3835-304 and unblinding of EN3835-302/303, subjects who received EN3835 in EN3835-302 or

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	each category, the following Exclusion Criteria apply beyond Day 180.	EN3835-303 will be placed into one of three categories based on their responder status of each of their buttocks at Day 71 in study EN3835-302 or EN3835-303 (Section 10.1). Investigators, subjects and all site personnel will be blinded to the treatment that the subjects received in the double-blind studies until assessments at the Day 180 visit of study EN3835-304 are completed; even if this visit occurs after the EN3835-302/303 studies are unblinded by Endo. Investigator, subjects and site personnel will be unblinded on Day 180 of study EN3835-304 after Day 180 assessments are completed or at an Unscheduled Visit, pending when database lock and unblinding of studies EN3835-302/ 303 occurs relative to Day 180 of this current study EN3835-304. For each category, the following Inclusion and Exclusion Criteria apply beyond the day that the investigator, subject, and site personnel are unblinded:
Section 11.2.2 Category I Subjects (Post Unblinding of EN3835-302/303)	Added	Exclusion Criteria for Subjects Whom opt for Observations Only (ie, no retreatment): None
	A Category I subject will not receive additional treatments and will be moved to Category III status if she: 1. Is unwilling to receive one additional course of open-label retreatment (3 treatment visits) for EFP with EN3385 2. Has any of the following systemic conditions: a. Coagulation disorder b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there has been no recurrence in at least 5 years c. History of keloidal scarring or abnormal wound healing d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases should be discussed with the Medical Monitor e. Evidence of clinically significant abnormalities on physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory values 3. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome	Deleted

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	b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Severe skin laxity, flaccidity, and/or sagging e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer f. Has a tattoo and/or a mole located within 2 cm of the site of injection 4. Requires the following concomitant medications before or during participation in retreatment portion the trial: a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug 5. Has used any of the following for the treatment of EFP on a buttock within the timelines identified below or intends to use any of the following at any time during the course of the study, including (but not limited to): a. Liposuction in a buttock since completion of the double-blind study b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock since completion of the double-blind study. c. Any investigational treatment for EFP on a buttock since completion of the double-blind study d. Endermologie™ or similar treatments within a buttock since completion of the double-blind study e. Massage therapy within a buttock during the 3-month period before retreatment with study drug f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before retreatment with study drug 6. Prior to and during the course of retreatment (Visit 2 through Visit 6), is presently nursing or providing breast milk 7. Prior to and during the course of retreatment (Visit 2 through Visit 6), intends to become pregnant during the study 8. Prior to and during the course of retreatment (Visit 2 through Visit 6), intends	

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	to use tanning spray or tanning booths during the study 9. Has received an investigational drug or treatment within 30 days before retreatment with study drug 10. Has a known systemic allergy to collagenase or any other excipient of study drug 11. Has received any collagenase treatments at any time since completion of the double-blind study 12. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for Category I retreatment.	
Section 11.2.3 Category II Subjects (Post Unblinding of EN3835-302/303)	Added	Exclusion Criteria for Subjects Whom opt for Observation Only (ie, no retreatment):
	1. Intends to or has used any of the following for the treatment of EFP on a buttock at any time during the course of the study, including (but not limited to):	1. Intends to or has used any of the following for the treatment of EFP on a buttock at any time during the course of the study:
	a. Liposuction in a buttock during the 12-month period before injection of study drug	a. Liposuction in a buttock
	b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock during the 12-month period before injection of study drug	b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock
	c. Any investigational treatment for EFP on a buttock during the 12-month period before injection of study drug	c. Any investigational drug or treatment for EFP on a buttock (other than treatment in study EN3835-302/303)
	d. Endermologie™ or similar treatments within a buttock during the 6-month period before injection of study drug	d. Endermologie™ or similar treatments within a buttock
	e. Massage therapy within a buttock during the 3-month period before injection of study drug	e. Massage therapy within a buttock during the 3-month period before observational visit
	f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before injection of study drug	f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before observational visit
	2. Has received an investigational drug or treatment within 30 days before injection of study drug	2. Has received an investigational drug or treatment (other than treatment in study EN3835-302/303)
	3. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study	3. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study

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Section 11.2.5 Retreatment Subjects (Eligible Subjects Whom opt to Receive Retreatment)	Added	Exclusion Criteria for Subjects Whom opt to Receive Retreatment: 1. Has any of the following systemic conditions: a. Coagulation disorder b. Evidence or history of malignancy (other than excised basal-cell or squamous-cell carcinoma) unless there has been no recurrence in at least 5 years c. History of keloidal scarring or abnormal wound healing d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases should be discussed with the Medical Monitor e. Evidence of clinically significant abnormalities on physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory values 2. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Severe skin laxity, flaccidity, and/or sagging e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer f. Has a tattoo and/or a mole located within 2 cm of the site of injection 3. Requires the following concomitant medications before or during participation in retreatment portion the trial: a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before or 7 days after injection of study drug 4. Has used any of the following for the treatment of EFP on a buttock within the timelines identified below or intends to use any of the following at any time during the course of the study: a. Liposuction in a buttock since completion of the double-blind study b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment;

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		cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock since completion of the double-blind study c. Any investigational treatment for EFP on a buttock since completion of the double-blind study d. Endermologie™ or similar treatments within a buttock since completion of the double-blind study e. Massage therapy within a buttock during the 3-month period before retreatment with study drug f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before retreatment with study drug 5. Prior to and during the course of retreatment (Treatment Visit 1 through Treatment Visit 4), is nursing or providing breast milk 6. Prior to and during the course of retreatment (Treatment Visit 1 through Treatment Visit 4), intends to become pregnant during the study 7. Prior to and during the course of retreatment (Treatment Visit 1 through Treatment Visit 4), intends to use tanning spray or tanning booths during the study 8. Has received an investigational drug or treatment, other than treatment in study EN3835-302/303, within 30 days before retreatment with study drug
		9. Has a known systemic allergy to collagenase or any other excipient of study drug 10. Has received any collagenase treatments at any time since completion of the double-blind study 11. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for retreatment
Section 12.1 Study Visits	The Schedule of Events to be performed at each visit prior to unblinding of studies EN3835-302/303 is shown in Section 5.1. Following completion and unblinding of EN3835-302/303, subjects will be placed into one of 3 categories based on their treatment and responder status (Section 10.1), and the Schedule of Events for subject categories I, II, and III are shown in Section 5.2, Section 5.3, and Section 5.4, respectively.	The Schedule of Events for all subjects up through 180 days following studies EN3835-302/303 is provided in Section 5.1. Beyond Day 180, the Schedule of Events for subjects classified as categories I and II and who are eligible and opt to receive retreatment is provided in Section 5.2 and in observational phase of study Section 5.3. The Schedule of Events for subjects in Category II who are not eligible for retreatment, or are in Category I and II and who are eligible but opt not to have

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		retreatment, is provided in Section 5.3. The Schedule of Events for Category III subjects is shown in Section 5.4.
Section 12.1.2 Subject Screening	Added	If the Screening Visit for a subject is within 14 days of the subject's Day 71 of study EN3835-302/303, the Screening Visit assessments for a subject will be pre-populated by a data transfer of the results of assessment of Day 71 (and height and Fitzpatrick scale rating of Day 1) of study EN3835-302/303 for that subject. If the Screening Visit for a subject is greater than 14 days of the subject's Day 71 of study EN3835-302/303, the Screening Visit assessments will be performed as detailed in Section 5.1 with only the subject ID and Fitzpatrick scale rating transferring from Day 1 of study EN3835-302/303 and pre-populating the EDC of study EN3835-304. All medical history occurring between completion of study EN3835-302/303 and the Screening Visit of study EN3835-304 will be considered adverse events and will be recorded and evaluated for seriousness and severity (see as appropriate, Section 14.1.1, Adverse Events or Section 14.1.2, Serious Adverse Events).
Section 12.1.3 Medical History	During the screening period, the Day 360 Visit, and at all Visits at or beyond Day 540, the Investigator or qualified designee will obtain a medical history from each subject that includes relevant diagnoses and/or procedures/therapies with onset/resolutions dates. Medical histories should also include history of EFP (start date and family history), and history of tobacco and alcohol use (never, current, former).	Since this is a long-term rollover study for subjects that participated and completed the double-blind study (EN3835-302 or EN3835-303), in which the subjects' medical history was collected; there will be no medical history collected for study EN3835-304.
Section 12.1.5 Day 180 Visit	Subjects will return at 180 days (±14 days) following initial injection of EN3835 in one of the double-blind studies for cellulite severity evaluation visits of the open-label study. Assessments to be completed at these visits are detailed in Section 5.1. Following unblinding of EN3835-302/303, subjects who received placebo will be discontinued, and subjects who received active EN3835 will be classified into 3 categories based on responder status.	Subjects will return at 180 days (±14 days) following their Screening Visit (Day 71 of the double-blind studies (EN3835-302 or EN3835-303)) for cellulite severity assessments. All assessments will be completed as detailed in Section 5.1 prior to unblinding of the subject's treatment assignment in the double-blind study. Local safety assessments (Section 14.6.1) and adverse events will be monitored (Section 14). If unblinding of drug treatment in EN3835 302/303 occurs by the Sponsor prior to a subject's Day 180 visit, Investigators, subjects and site personnel will remain blinded to the subject's drug treatment in the double-blind studies until after the Day 180

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		assessment have been completed. After assessments are completed, unblinding will occur at the site and subjects who received placebo will be discontinued, and subjects who received active EN3835 will be classified into one of three categories based on responder status of each of their buttocks in the double-blind study (Section 10.1). If the subject is classified to a classification and has ratings that qualify for retreatment (ie, all Category I subjects will be offered retreatment; Category II subjects that have lost 1-composite level of response (ie, at least a 1-level worsening of both PR-PCSS and CR-PCSS in at least one buttock). If there is a composite worsening of cellulite severity of 1-level (ie, worsening of both the PR-PCSS and CR-PCSS by at least 1 severity levels) detected in a Category II subject, the confirmation of loss of response will be established during a follow-up visit ~2 weeks after the loss of response is detected at Day 180 as described in Section 12.2.2.3 (Confirmation Visit). If a Category I subject accepts the offer of retreatment at the Day 180 visit, Screening B of the Treatment Phase of the protocol may occur on the same day as the Day 180 Visit. If the loss of response in a Category II subject is confirmed and the subject accepts the offer of retreatment at the Confirmation Visit, Screening B of the Treatment Phase may occur on the same day as the Confirmation Visit. If the loss of response is not confirmed, the subject will be considered to not have lost response and will not be offered retreatment. If the unblinding has not occurred by a subject's Day 180 visit, an Unscheduled Visit will be arranged after unblinding has occurred (see Section 12.4) and the subjects will be classified at this Unscheduled Visit or, if received placebo, will be discontinued. If a Category I subject decides to accept the offer of retreatment, the subject may be screened (Screening B Visit of the Treatment Phase) during the Unscheduled Visit. If there is a composite worsening of cellulite severity of 1-level (ie, worsening of both the PR-PCSS and CR-PCSS by at least 1 severity levels) detected in a Category II subject during the Unscheduled Visit, the confirmation of loss of response will be established during a follow-up visit ~2 weeks after the loss of response is detected as

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		described in Section 12.2.2.3 (Confirmation Visit). If the loss of response in a Category II subject is confirmed and the subject accepts the offer of retreatment at the Confirmation Visit, Screening B of the Treatment Phase may occur on the same day as the Confirmation Visit. If the loss of response is not confirmed, the subject will be considered to not have lost response and will not be offered retreatment. As stated in Section 10.1, either on Day 180 Visit after assessments have been completed or at an Unscheduled Visit, once the study blind is broken, the EN3835-302/303 placebo subjects will be discontinued, and subjects who received active EN3835 in their respective double-blind study will be classified into one of three categories based on their response in the double-blind study.
Section 12.2 Study Visits (Post Unblinding of EN3835-302/ 303)	Once the study blind is broken, the EN3835-302/303 placebo subjects will be discontinued, and subjects who received active EN3835 in their respective double-blind study will be classified into one of three categories (Section 10.1), based on their response in the double-blind study.	Deleted
Section 12.2 Category I Subjects and Category II Subjects Visits (Post Unblinding of EN3835-302/ 303	Assessments to be completed at these visits are detailed in Section 5.2. Subjects are to return for a course of retreatment one year after the Day 71 Visit of the double-blind study, and will be assessed at regular intervals thereafter for cellulite severity and safety until they have completed approximately 5 years (1800 days) from Day 71 of the double-blind study. At these visits, the region previously treated with EN3835 in the double-blind EN3835-302/ 303 study will be evaluated (Section 5.2). The duration of response for composite 1-level responders (ie, Category I) will also be assessed at 180 days after the Day 71 Visit of the double-blind study. Loss of response is defined as a composite worsening of cellulite severity back to baseline levels (on both the PR-PCSS and CR-PCSS).	Assessments to be completed at these visits are detailed in Section 5.2 (Treatment Assessments) and in Section 5.3 (Observation Assessments).
	Added	Beginning at Day 180 (ie, approximately 6 months after Day 71 Visit of the double-blind study); after Day 180 assessments have been completed in a blinded fashion, all Category I subjects will be offered a course of retreatment. Category II subjects who have shown a 1-level composite reduction of response compared to

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		their Day 71 from EN3835-302/302 improvement will be offered a course of retreatment; and assessments to be completed at these Treatment Assessments are detailed in Section 5.2. After completing Day 71 of the retreatment in this open-label study, the subjects will be assessed at intervals for cellulite severity and safety as detailed in Section 5.3 until they have completed approximately 5 years (1800 days) from Day 71 of the double-blind study. Category II subjects that have not shown a 1-level composite reduction (ie, have maintained a successful response), and/or Category I and/or Category II subjects who are eligible for a retreatment course but opt not to receive retreatment will be assessed at intervals (Section 5.3) for cellulite severity and safety until they have completed approximately 5 years from Day 71 of the double-blind study. If the subject's buttocks become eligible for retreatment based on the ratings of an observational visit and if they have not already received a course of retreatment, they will be offered retreatment up to including Observational Visit 6 (Month 48); no retreatments will be offered after Visit 6. The TRR for composite 1-level responders(ie, Category I) will also be assessed at 180 days after the Day 71 Visit of the double-blind study as well as after Treatment Visit 4 (Retreatment Day 71) of this open-label study for those buttocks that are retreated. Buttocks not retreated will be assessed at each of the observation visits as shown in Section 5.3. TRR is defined as a 1-level composite worsening of cellulite severity levels (on both the PR-PCSS and CR-PCSS). If a treatment period eclipses (or overlaps) a scheduled observational visit, the observational visit will be skipped and the subject will re-enter the observational schedule at the next interval visit. For example, if a subject initiated retreatment on Day 351 (which would then be Treatment Visit 1), the treatment period would proceed for approximately 71 days until Day 421 (Treatment Visit 4) and the Observational Visit at Day 360 would be skipped; the subject's next observational visit would be Day 540. Treatments will not be offered to any subject after Visit 6 (Day 1440 ±30 days; Month 48 ± 1 month).

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Section 12.2.1 Treatment Assessments (Treatment is Optional for Eligible Subjects)	12.2.1.1. Visit 2 (Screening B)	12.2.1.1. Screening B (Days -14 to -1 Relative to Treatment Visit 1)
	The following procedures will be performed and documented during Visit 2:	The following procedures will be performed and documented during Screening B:
	4. Subjects will get instruction on the use of the PR-PCSS (Section 13.1.2.1)	4. Subjects will get instruction on the use of the PR-PCSS (Section 13.1.2.1) and review training and use materials.
	6. Patient Reported Cellulite Impact Scale (PR-CIS) assessment (Section 13.1.2.2); note this assessment is of both left and right buttocks rather than each individual buttock	6. Subjects will review subject cellulite assessment training and use materials prior to use of the S-GAIS, PR-CIS, Subject Satisfaction with Cellulite Treatment Assessment, and the SSRS.
	9. After the subject has completed the PR-PCSS ratings, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (Section 13.1.2.5); the subject is blinded to these ratings. The ratings from the PR-PCSS and CR-PCSS will be used to assess eligibility of the buttocks for retreatment (to be eligible, a buttock must have a composite score of at least 2 on the PR-PCSS and CR-PCSS).	7. Subject Global Aesthetic Improvement Scale (S-GAIS) (Section 13.1.2.2); subjects will rate each of their two buttocks while viewing pretreatment images from Day 1 of the double-blind study (EN3835-302/303)
	10. Medical history including EFP history (Section 12.1.3)	8. Patient Reported Cellulite Impact Scale (PR-CIS) assessment (Section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock
	12. Physical examination including measurement of body weight (Section 14.11)	11. After the subject has completed the PR-PCSS ratings and after the Investigator has reviewed the training and use material for the CR-PCSS, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (Section 13.1.2.6); the subject is blinded to these ratings. The ratings from the PR-PCSS and CR-PCSS will be used to assess eligibility of the buttocks for retreatment
		13. Physical examination including measurement of body weight and height (Section 14.11)
Section 12.2.1.1 Screening B (Days -14 to -1 Relative to Treatment Visit 1)	Added	15. 12-lead ECG (Section 14.10)
		17. Injection site reactions/local tolerability in the buttocks (Section 14.6.1)
Section 12.2.1.2 Selecting and Marking Dimples during Treatment Visits	Category I subjects eligible for retreatment can receive up to 3 retreatment visits of study drug as outlined in Section 5.2 unless the buttock is dimple-free (score of 0 on CR-PCSS as reported by the Investigator) at Visit 4 (Day 395) and/or Visit 5 (Day 416).	Category I subjects and Category II subjects eligible for retreatment can receive up to 3 retreatment visits of study drug as outlined in Section 5.2 unless the buttock is dimple-free (score of 0 on CR-PCSS as

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		reported by the Investigator) at Treatment Visit 2 and/or Treatment Visit 3.
	If no injections in a particular buttock (right or left) are given at Visit 4, subjects will still be assessed for retreatment in the contralateral buttock at Visit 4 if the buttock was retreated at Visit 3, and when they return for Visit 5, each of the buttocks will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS). If the Investigator rates either or both of the buttocks greater than 0 on the CR-PCSS, injections at Visit 5 should be given.	If no injections in a particular buttock (right or left) are given at Treatment Visit 2, subjects will still be assessed for retreatment in the contralateral buttock at Treatment Visit 2 if the buttock was retreated at Treatment Visit 1, and when they return for Treatment Visit 3, each of the buttocks will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS). If the Investigator rates either or both of the buttocks greater than 0 on the CR-PCSS, injections at Treatment Visit 3 should be given.
Section 12.2.1.3 Digital Photography during Treatment Visits 1, 2, and 3	12.2.1.3. Digital Photography during Visits 3, 4, 5 During each retreatment visit, each of the eligible buttocks to be retreated will be photographed before and after marking dimples and injections sites while the subject is standing in a consistent, standardized relaxed pose as described in Section 13.1.1. In addition, a buttock that is not retreated will be photographed and monitored.	12.2.1.3. Digital Photography during Treatment Visits 1, 2, and 3 During each retreatment visit, each of the buttocks will be photographed before and after marking dimples and injections sites while the subject is standing in a consistent, standardized relaxed pose as described in Section 13.1.1.
Section 12.2.1.4.1 Treatment Visit 1: Pre-Injection	12.2.1.4. Visit 3 (Day 374)	12.2.1.4. Treatment Visit 1
	12.2.1.4.1. Visit 3: Pre-Injection	12.2.1.4.1. Treatment Visit 1: Pre-Injection
	For each subject, the areas eligible for retreatment will be determined via IWRS based on the PR-PCSS/CR-PCSS scores obtained during Visit 2. Both buttocks will be photographed during the retreatment visits.	For each subject, the areas eligible for retreatment will be confirmed via the IWRS based on the PR-PCSS/CR-PCSS ratings obtained during Treatment Visit 1. Each buttock will be photographed during the retreatment visits.
	2. Subjects will get instruction on the use of the PR-PCSS (Patient Instructions for Use of PR-PCSS)	2. Subjects will get instruction on the use of the PR-PCSS (Patient Instructions for Use of PR PCSS) and review training and use materials
	Added	4.The Investigator will review training and materials for the use of the CR-PCSS
Section 12.2.1.4.2 Treatment Visit 1: Injection and Post-injection	12.2.1.4.2. Visit 3: Injection and Post-injection	12.2.1.4.2. Treatment Visit 1: Injection and Post-injection
Section 12.2.1.5.1 Treatment Visits 2 and 3: Pre-injection	12.2.1.5. Visits 4 and 5 (Day 395 and Day 416)	12.2.1.5. Treatment Visits 2 and 3 (Day 22 ± 3 days and Day 43 ± 3 days)
	12.2.1.5.1. Visits 4 and 5: Pre-injection	12.2.1.5.1. Treatment Visits 2 and 3: Pre-injection
	6. Subject Cellulite Assessments of each of the buttocks receiving retreatment using the photographic image of each buttock before marking dimples and injection sites	6. Subject Cellulite Assessments, after review of training and use materials, of each of the buttocks using the photographic image of each buttock before marking dimples and injection sites

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	7. Investigator Cellulite Assessments live of each of the buttocks receiving retreatment prior to marking dimples and injection sites using:	7. Investigator Cellulite Assessments conducted, after review of training and use material, of each of the buttocks receiving retreatment prior to marking dimples and injection sites using
Section 12.2.1.6 Treatment Visit 4 (Day 71+ 5 days)	12.2.1.6. Visit 6 (Day 444)	12.2.1.6. Treatment Visit 4 (Day 71+ 5 days)
	The following procedures will be performed at Visit 6:	The following procedures will be performed at Visit 4:
	2. Measurement of body weight and height	2. Measurement of body weight
	Added	6. Subject will review training and use materials for the PR-PCSS, S-GAIS, PR-CIS, Subject Satisfaction with Cellulite Treatment Assessment, and SSRS
	b. Patient Reported Cellulite Impact Scale (PR-CIS) assessment (Section 13.1.2.2); note this assessment is of both left and right buttocks rather than each individual buttock.	b. Subject Global Aesthetic Improvement Scale (S-GAIS) (Section 13.1.2.2); subjects will rate each of their two buttocks while viewing pretreatment images from Day 1 of the double-blind study (EN3835-302/303)
	7. Subject will complete the Subject Satisfaction with Cellulite Treatment Assessment (Section 13.1.2.3): note this assessment is of both left and right buttocks rather than each individual buttock	7. Patient Reported Cellulite Impact Scale (PR-CIS) assessment (Section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock while viewing images from Treatment Visit 4 (Day 71) of EN3835-304.
	8. Subject will complete the Subject Self-Rating Scale (SSRS) (Section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock.	8. Subject will complete the Subject Satisfaction with Cellulite Treatment Assessment (Section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock and is conducted while viewing images from Treatment Visit 4.
	9. Investigator Cellulite Assessments of each of the buttock(s) receiving retreatment live using:	9. Subject will complete the Subject Self-Rating Scale (SSRS) (Section 13.1.2.5); note this assessment is of both left and right buttocks rather than each individual buttock.
	a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (Section 13.1.2.6)	10. Investigator Cellulite Assessments will be conducted, after the review of training and use material for the CR-PCSS, of each of the buttock(s) receiving retreatment using: a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (Section 13.1.2.6) After Treatment Visit 4, retreated subjects enter/re-enter the observational phase of the study with assessments of safety and TRR. If an observational visit was scheduled to occur during a Treatment Phase visit (Screening B through Treatment Visit 4), the observational visit would be skipped and the subject would enter/re-enter the Observation Phase visits at the next interval visit.

Section	Original Text	Revised Text
12.2.1.7. Visits 7-11/EOS	Visits 7-11/EOS and all text in this Section	Deleted
Section 12.2.2.1 Visit 2 (Day 360 relative to Day 71 of the double-blind study)	12.2.2.1. Visit 2 (Day 360)	12.2.2.1. Visit 2 (Day 360 relative to Day 71 of the double-blind study)
	4. Subjects will get instruction on the use of the PR-PCSS (Section 13.1.2.1)	4. Subjects will get instruction on the use of the PR-PCSS (Section 13.1.2.1) and review training and use materials for the PR-PCSS, the PR-CIS, the SSRS and the Subject Satisfaction with Cellulite Treatment assessments
	Added	6. Subject Global Aesthetic Improvement Scale (S-GAIS) (Section 13.1.2.2); subjects will rate each of their two buttocks while viewing pretreatment image from Day 1 of the double-blind study (EN3835-302/303)
	9. After the subject has completed the PR PCSS ratings, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (Section 13.1.2.5); the subject is to remain blinded to these ratings	10. After the subject has completed the PR PCSS ratings and after the Investigator reviews the training and use materials for the CR-PCSS, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (Section 13.1.2.6); the subject is to remain blinded to these ratings
	Added	13. Local safety assessments (Section 14.6.1)
	10.Medical history including EFP history (Section 12.1.3)	Deleted
Section 12.2.2.2 Visits 3-7/EOS (Day 540-Day 1800 /EOS)	12.2.2.2. Visits 3-10/EOS (Day 540 – Day 1800/EOS)	12.2.2.2. Visits 3-7/EOS (Day 540 – Day 1800/EOS)
	Added	4. Subjects will get instruction on the use of the PR-PCSS (Section 13.1.2.1) and review training and use materials for the PR-PCSS, S-GAIS, PR-CIS, SSRS and the Subject Satisfaction with Cellulite Treatment assessments
		5.b. Subject Global Aesthetic Improvement Scale (S-GAIS) (Section 13.1.2.2); subjects will rate each of their two buttocks while viewing pretreatment image from Day 1 of the double-blind study (EN3835-302/303)
	7. Medical history including EFP history (Section 12.1.3)	Deleted
	Added	11. Check ePRO for a potential requirement for a confirmation visit.
		12. Local safety assessments (Section 14.6.1)
Section 12.2.2.3 Confirmation Visits	Durability of a ≥2-level composite improvement in cellulite severity compared to the baseline level established during the double-blind study will be assessed by both the PR-PCSS and the CR-PCSS. If, during the study, there is a composite worsening of cellulite severity back to baseline levels	Time to reduction of a ≥1 level and/or ≥2-level composite improvement in cellulite severity compared to the level at Day 71 of the double-blind study will be assessed by both the PR-PCSS and the CR-PCSS. If, during the study, there is a composite worsening of cellulite severity of 1-level

Section	Original Text	Revised Text
	(ie, worsening of both the PR-PCSS and CR-PCSS back to baseline levels), the confirmation of loss of response will be established during a follow-up visit ~2 weeks after the loss of response is first detected.	(ie, worsening of both the PR-PCSS and CR-PCSS by 1 severity levels), the confirmation of loss of response will be established during a follow-up visit ~2 weeks after the loss of response is first detected.
	2. Subject Cellulite Assessment of each of the two buttocks using the photographic image (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using:	2. Subject Cellulite Assessment of each of the two buttocks, after reviewing the training and use materials, using the photographic image (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using:
	3. Investigator Cellulite Assessments of each of the buttocks live using:	3. Investigator Cellulite Assessments of each of the buttocks, after reviewing the training and use material, using:
	NOTE: Subjects showing a confirmed composite worsening of cellulite severity back to baseline levels will no longer require efficacy assessments, but should continue with annual safety and immunogenicity assessments as a Category III subject (Days 360, 720, 1080, 1440, and 1800).	NOTE: Subjects showing a confirmed composite worsening of cellulite severity of 1-level will be offered retreatment and will continue with annual safety and immunogenicity assessments for up to 5 years after Day 71. Subjects who do NOT show a confirmed composite worsening of cellulite will be considered to not have a worsening, will not be offered retreatment, and will continue with annual safety and immunogenicity assessment for up to 5 years after Day 71.
Section 12.3 Category III Subjects Visits (Post Unblinding of EN3835-302/ 303)	12.2.3. Category III Subjects	12.3. Category III Subjects Visits (Post Unblinding of EN3835-302/303)
	Category III subjects are to return every 360 days until they have completed 1800 days (5 years) following completion of the double-blind study for safety evaluations.	Category III subjects are to return every 6 months during the first two years and then annually until they have completed 1800 days (5 years) following Day 71 of the double-blind study for safety evaluations.
	3. Medical history including EFP history (Section 12.1.3)	Deleted
	Added	3. Local safety assessments (Section 14.6.1)
Section 12.4 Unscheduled Visit	Added	If any subject needs to return to the site prior to her next scheduled visit, site staff should follow the Unscheduled Visit procedures outlined in Section 5. Site staff may conduct additional study procedures if required. If unblinding of Investigator, subject and site personnel to the treatment that the subject received in the double-blind study EN3835-302/303 does not occur on Day 180 Visit after all assessments are completed, then an unscheduled visit may be arranged to unblind the subject to the treatment received. Following unblinding of EN3835 302/303, subjects who received placebo will be discontinued, and subjects who received active EN3835 will be classified into one of

Section	Original Text	Revised Text
		three categories based on responder status (Section 10.1) and proceed as described in Section 12.1.
	All prior medications taken within 90 days before randomization will be recorded. All medications (including over-the-counter medications) taken by the subject on Day 1 through the end of the study must be recorded. Any prior treatments (medications or procedures) for EFP through the end of the study must be recorded on the appropriate eCRF page. Any prior use of XIAFLEX should also be recorded.	All prior medications will be recorded; the word 'prior' refers to the period from the last visit from the double-blind study through the signing of the informed consent in the EN3835-304 study. All concomitant medications (including over-the-counter medications) including those to treat EFP, taken by the subject during the course of the EN3835-304 study (ie, after informed consent for EN3835-304 is signed) will be recorded.
Section 12.5.1 Prohibited Medications or Procedures	For Category I subjects, the following medications are prohibited between Day 360 and Day 444 (ie, the retreatment phase of the study, Table 4): anticoagulants (warfarin, heparin, direct thrombin inhibitors, Factor X inhibitors) and antiplatelet agents (aspirin >150 mg/day and P2Y12 inhibitors, such as clopidogrel), which can cause additional bruising.	For Category I subjects and eligible Category II subjects who opt for retreatment, the following medications are prohibited during the retreatment phase of the study (Table 4): anticoagulants (warfarin, heparin, direct thrombin inhibitors, Factor X inhibitors) and antiplatelet agents (aspirin >150 mg/day and P2Y12 inhibitors, such as clopidogrel), which can cause additional bruising.
	Procedures listed in exclusion criterion #5 for Category I subjects, and exclusion criterion #1 for Category II subjects are prohibited for Category I and Category II subjects during the study, respectively.	Procedures listed in exclusion criterion #1 for all subjects up through Day 180 Visit, exclusion criterion #4 for Category I subjects, and exclusion criterion #1for Category II subjects are prohibited for all subjects up through Day 180 visit, Category I and Category II subjects during the study, respectively.
	For Category II and Category III subjects, this is an observational study to assess long-term safety and/or durability of response. Since no additional treatments are administered, there are no prohibited medications. Note that the use of creams, procedures, etc as outlined in the exclusion criteria (Section 11.2) is prohibited for the duration of the study.	For Category I, Category II and Category III subjects, this is an observational study to assess long-term safety and/or TRR. The use of creams, procedures, etc as outlined in the exclusion criteria (Section 11.2) is prohibited for the duration of the study. There are no additional prohibited medications.
Section 12.6 Treatment Compliance	Category I subjects will receive study drug administered by an Investigator at the Investigator's site.	Category I subjects and/or eligible Category II subjects may receive study drug administered by an Investigator at the Investigator's site.
	For Category II and Category III subjects, this study is observational in nature, and no additional treatments are to be administered.	For Category III subjects and Category I and Category II subjects that opt not to receive treatment, this study is observational in nature, and no additional treatments are to be administered.
Section 13.1.1 Digital Photography	After unblinding of the double-blind studies EN3835-302/303, photography will be limited to Category I and Category II subjects.	After Day 180 Visit and unblinding of the double-blind studies EN3835-302/303, photography will be limited to Category I and Category II subjects.

Section	Original Text	Revised Text
Section 13.1.2.1 Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	The scale is a 5-level photonumeric scale developed specifically for patients and used by the subject to assess the severity of their cellulite by viewing digital images of each of their buttocks (or thighs, as applicable) captured by photography at the visit; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the subject in the assessments. At Screening (eg, Day 71/EOS of the double-blind study) and at the beginning of each visit where photography is to be captured, subjects will have digital photographs taken of each of their buttock(s) and/or thigh. Subjects will be given instructions in the proper use (Patient Instructions for Use of PR-PCSS) of the PR-PCSS and then perform the PR-PCSS for each of the targeted areas (Appendix B). While viewing the digital images of each of their buttocks/thigh on a standardized computer monitor and using the appropriate PR-PCSS for buttock or thigh, subjects will be instructed to answer the following question for each buttock	The scale is a 5-level photonumeric scale developed specifically for patients and used by the subject to assess the severity of their cellulite by viewing digital images of each of their buttocks captured by photography at the visit; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the subject in the assessments. At Screening (eg, Day 71/EOS of the double-blind study) and at the beginning of each visit where photography is to be captured, subjects will have digital photographs taken of each of their buttock(s). Subjects will be given instructions in the proper use (Patient Instructions for Use of PR-PCSS) of the PR-PCSS, will review training and use material, and then perform the PR-PCSS for each of the targeted areas (Appendix B). While viewing the digital images of each of their buttocks on a standardized computer monitor and using the PR-PCSS for buttock, subjects will be instructed to answer the following question for each buttock:
Section 13.1.2.2 Subject Global Aesthetic Improvement Scale (S-GAIS)	Added	13.1.2.2. Subject Global Aesthetic Improvement Scale (S-GAIS) At each of the visits designated to capture the S-GAIS in Section 5.1, Section 5.2, and Section 5.3, subjects will review training and use materials for S-GAIS, and complete the S-GAIS for each of the buttocks as described below using the pretreatment Day 1 digital image (Baseline) from the double-blind studies (EN3835-302/303) of each of the buttocks for comparison. All treated subjects will be instructed to answer the following question for each buttock: *How would you rate the appearance of your treated cellulite after treatment?* The S-GAIS assessment will occur after the subject has completed the PR-PCSS assessment to avoid introducing potential bias to the static PR-PCSS assessment. The subject will view each of their pretreatment Day 1 digital images from the double-blind study (EN3835-302/303) alongside their current study visit digital images of each of their buttocks to aid in the assessment (Table 5). Subjects will provide a rating from those below that best represents their answer for each treated buttock.

Section	Original Text	Revised Text
		This variable will be entered directly into the ePRO system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
		Table 5: Subject Global Aesthetic Improvement Scale (S-GAIS) Rating - Response - Option - Description +3 Very much improved My treated cellulite looks very much better. +2 Much improved My treated cellulite looks much better, but additional treatment would slightly improve the result. +1 Improved My treated cellulite looks better, but additional treatment is necessary. 0 No change My treated cellulite looks essentially the same as it did originally. −1 Worse My treated cellulite looks worse than it did originally. −2 Much worse My treated cellulite looks much worse than it did originally. −3 Very much worse My treated cellulite looks very much worse than it did originally.
Section 13.1.2.3 Patient Reported Cellulite Impact Scale (PR-CIS)	At each of the visits designated to capture the PR-CIS in Section 5.1, Section 5.2, and Section 5.3, subjects will be instructed to answer 6 questions related to the areas selected for treatment on their buttocks on the Patient Reported Cellulite Impact Scale (Appendix D).	At each of the visits designated to capture the PR-CIS in Section 5.1, Section 5.2, and Section 5.3; subjects will review training and use materials, and will be instructed to answer 6 questions related to the areas selected for treatment on their buttocks on the Patient Reported Cellulite Impact Scale (Appendix D) while viewing digital images of their buttocks.
	The PR-CIS assesses the visual and emotional impact of cellulite (happy, bothered, self-conscience, embarrassed, looking older or looking overweight or out of shape) using a 6-question survey, with each question rated from 0 (not at all) to 10 (extremely).	The PR-CIS assesses the visual and emotional impact of cellulite (happy, bothered, self-conscious, embarrassed, looking older or looking overweight or out of shape) using a 6-question survey, with each question rated from 0 (not at all) to 10 (extremely).
	Added	This variable will be entered directly into the ePRO system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable
Section 13.1.2.4 Subject Satisfaction with Cellulite Treatment Assessment	At the designated visits, subjects will be instructed to answer a question related to their treated buttocks. Subjects will be given a list of responses and they will provide a rating from those below that best represents their answer (Table 5).	At the designated visits, subjects will review training and use materials and will be instructed to answer a question related to their treated buttocks while viewing digital images of their buttocks. Subjects will be given a list of responses and they will provide a rating from those below that best represents their answer (Table 6).
	This variable will be entered directly into the EDC system, thus the electronic database	This variable will be entered directly into the ePRO system, thus the electronic database

Section	Original Text	Revised Text
	will serve as the direct point of data capture and will serve as source for this variable.	will serve as the direct point of data capture and will serve as source for this variable.
Section 13.1.2.5 Subject Self-Rating Scale (SSRS)	The patient will be asked to respond to the question related to the satisfaction with appearance of the cellulite on their buttocks.	The subject will review training and use materials for the SSRS. The subject will be asked to respond to the question related to the satisfaction with appearance of the cellulite on their buttocks
	This variable will be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.	This variable will be entered directly into the ePRO system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
Section 13.1.2.6 Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	The scale is a 5-level photonumeric scale developed specifically for clinicians and used by the Investigator to assess the severity of the subject's cellulite in each buttock (or thigh, where applicable) by live assessments; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the Investigator in the assessments. Investigators will be trained and qualified on the use of the CR-PCSS prior to assessing any subjects. At the Day 71 visit during the double-blind study (which also serves as the Screening visit for the current study), the Investigator will determine severity of cellulite of each of the two buttocks via live assessment of the subject using the CR PCSS for buttock (Appendix C) after the subject has completed her self-assessment using the PR-PCSS (Appendix C).	The scale is a 5-level photonumeric scale developed specifically for clinicians and used by the Investigator to assess the severity of the subject's cellulite in each buttock by live assessments; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the Investigator in the assessments. Investigators will be trained and qualified on the use of the CR-PCSS prior to assessing any subjects. Investigators will review training and use materials at each visit prior to the use of the CR-PCSS. At the Day 71 visit during the double-blind study (which also serves as the Screening visit for the current study), the Investigator will determine severity of cellulite of each of the two buttocks via live assessment of the subject using the CR PCSS for the buttock (Appendix C) after the subject has completed her self-assessment using the PR-PCSS for the buttock (Appendix B).
Section 14.5.1 Reporting Adverse Events	Conditions existing prior to screening will be recorded as part of the subject's medical history.	Deleted
Section 14.6.1 Adverse Events of Special Interest	In addition, local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration, will be recorded and evaluated for seriousness and severity (see as appropriate, Section 14.1.1, Adverse Events or Section 14.1.2, Serious Adverse Events)	In addition, local AEs associated with the injection site (whether the site was injected in the double-blind study (EN3835/302/303) or in this open-label study (EN3835-304)), including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, peau d'orange changes) cutaneous adverse events, will be recorded and evaluated for seriousness and severity (see as appropriate, Section 14.1.1, Adverse Events or Section 14.1.2, Serious Adverse Events).
Section 14.7 Clinical Laboratory Determinations	For women of childbearing potential, a serum pregnancy test will be performed at the Day 71 visit from the double-blind study (EN3835-302 or EN3835-303), and urine pregnancy tests will be performed at the	For women of childbearing potential, a serum pregnancy test will be performed at the Day 71 visit from the double-blind study (EN3835-302 or EN3835-303), the results of which will be data transferred to the

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	other study visits (refer to Section 5.1 and Section 5.2). If necessary, additional urine pregnancy tests can be performed at any time during the study at the discretion of the Investigator. Urine pregnancy test kits will be supplied by the Sponsor.	Screening Visit of this open-label study if the Screening Visit occurs within 14 days of the Day 71 visit of the double-blind study. Additionally, a serum pregnancy test will be performed at the Screening B visit of any Category I and/or eligible Category II subject screening for the Treatment phase of the study. Urine pregnancy tests will be performed at the other study visits (refer to Section 5.1 and Section 5.2).
Section 14.8 Anti-AUX-I and Anti-AUX-II Antibodies	For Category I subjects receiving retreatment, a subset (based on every other sample from the Visit 6 [Day 444] upper and lower quadrants of binding antibody titers) of subject samples will be tested for neutralizing antibodies from these visits; additional samples will be retained.	For Category I subjects and/or eligible Category II subjects receiving retreatment, a subset (based on every other sample from the Treatment Visit 4 upper and lower quadrants of binding antibody titers) of subject samples will be tested for neutralizing antibodies from these visits; additional samples will be retained.
Section 14.9 Vital Signs	For Category I subjects receiving retreatment, vital signs will be assessed at the time points shown in Table 8 after the subject has rested for at least 5 minutes.	For Category I and/or eligible Category II subjects receiving retreatment, vital signs will be assessed at the time points shown in Table 9 after the subject has rested for at least 5 minutes.
Section 14.10 Electrocardiogram	No ECGs are to be performed during this study.	Performing a 12-lead electrocardiogram (ECG) is not necessary if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-302/303). If the date of Screening B visit is later than 12 months since obtaining the ECG in study EN3835-302/303, subjects will have a resting 12-lead ECG performed during the Screening B visit. A qualified physician will interpret, sign, and date the ECGs. Electrocardiogram assessments must be “within normal limits” or interpreted as “abnormal, not clinically significant” for the subject to be included in the study.
		Any ECG result meeting the investigator’s or Sponsor’s criteria for clinical significance will be recorded as an AE or SAE as appropriate (see Section 14.1.1, Adverse Events and Section 14.1.2, Serious Adverse Events).
Section 14.11 Physical Examination	Height and body weight will be measured at additional Visits for Category I subjects (in the absence of a full physical exam) as designated in Section 5.2.	Height and body weight will be measured at additional visits for Category I and retreatment-eligible Category II subjects (in the absence of a full physical exam) as designated in Section 5.2.
Section 17.1 Determination of Sample Size	Approximately 420 subjects completed the EN3835-302/303studies will rollover to this study. This sample size should be adequate	Approximately 420 active subjects who completed the EN3835-302/303studies will rollover to this study. This sample size

Section	Original Text	Revised Text
	to determine long-term safety and cellulite assessments of EN3835 for durability.	should be adequate to determine long-term safety and TRR of EN3835.
Section 17.2 Subject Populations	For subjects entering open-label study period, subjects who received active EN3835 in their double-blind studies (EN3835-302/ 303) will be classified into 3 categories: Category I: 1-level Composite Responders Category II: 2-Level Composite Responders Category III: Non-Composite Responders Based on subject category, two (2) populations are considered in the statistical analysis of the study: overall safety population and durability population.	For subjects entering the open-label study period, subjects who received active EN3835 in their double-blind study (EN3835-302/ 303) will be classified into one of three categories: Category I: 1-Level Composite Responders Category II: 2-Level Composite Responders Category III: Non-Composite Responders Based on subject category, two (2) populations are considered in the statistical analysis of the study: overall safety population and time to reduction in response population.
Section 17.2.1 Overall Safety Population	The overall safety population is defined as all rollover subjects who enter the open-label study period. This population will include all Category I, II, and III subjects. In addition, the safety data will be summarized by treatment period for those re-treated subjects with EN3835. Safety will be assessed for up to approximately 5 years from first exposure, and for Category I re-treated subjects, approximately 4 years following retreatment.	The overall safety population is defined as all subjects who enter the open-label study period and received EN3835 in EN3835-302 or EN3835-303. This population will include all Category I, II, and III subjects. All safety analyses will be based on this population. In addition, the safety data will be summarized by treatment period for those retreated subjects with EN3835.
Section 17.2.2 Day-180 Observational Population	Added	The Day-180 observational population will include all rollover subjects from studies EN3835-302/303. The safety analysis for the data obtained from Screening to Day 180 will be based on this population.
Section 17.2.3 Time to Reduction of Response (TRR) Population	17.2.2. Durability Population	17.2.3. Time to Reduction of Response (TRR) Population
	The durability population is defined as all subjects who have at least a 1 or 2-level improvement in both CR-PCSS and PR-PCSS scores/ratings during the double-blind study for either/both treated buttocks. This population will include Category I and II subjects. The durability data will be collected up to 6 months for Category I subjects and up to 5 years (1800 days following Day 71 of the double-blind study) for category II subjects.	The TRR population is defined as all subjects who have at least a 1-level or 2-level improvement in both CR-PCSS and PR-PCSS ratings during the double-blind study for either/both treated buttocks. This population will include Category I and II subjects.
Section 17.4 Demographics and Other Baseline Characteristics	Added	These data will be transferred from EN3835-302 and EN3835-303 and will pre-populate the relevant fields of the database for this open-label study.
Section 17.5 Efficacy Analyses	• PR-PCSS: a subject reported 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite).	• PR-PCSS: patient reported 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite).

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	• CR-PCSS: an investigator reported 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite).	• CR-PCSS: clinician reported 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite).
	• PR-CIS: a subject reported scale to assesses the visual and emotional impact of cellulite (happy, bothered, self-conscience, embarrassed, looking older or looking overweight or out of shape) using a 6-question survey, with each question rated from 0 (not at all) to 10 (extremely). A PR-CIS total score and an abbreviated PR CIS score (excluding question 5) will be derived from these 6 individual questions.	• PR-CIS: patient reported cellulite impact scale to assess the visual and emotional impact of cellulite (happy, bothered, self-conscious, embarrassed, looking older or looking overweight or out of shape) using a 6-question survey, with each question rated from 0 (not at all) to 10 (extremely). A PR-CIS total score and an abbreviated PR CIS score (excluding question 5) will be derived from these 6 individual questions.
		• Subject Global Aesthetic Improvement Scale (S-GAIS): a 7-level scale ranging from 3 (very much improved) to −3 (very much worse).
	All cellulite assessments will be done by treated areas, each quadrant will be evaluated separately.	All cellulite assessments will be performed on each individual treatment area. Treatment areas will be evaluated separately.
Section 17.5.1 Analyses	The analyses of cellulite assessments will be based on durability population. The durability of response will be defined from the accessing of the efficacy (Day 71 at EN3835-302/303) to the loss of response study visit.	The analyses of cellulite assessments will be based on the TRR population. The TRR will be defined from time of assessing the efficacy (Day 71 at EN3835-302/303) to the study visit at which a composite 1-level reduction of response in both PR-PCSS and CR-PCSS is observed.
	The defined endpoints will include:	The defined endpoints will include:
	• Proportion of subjects who lose their responses:	• Proportion of subjects with reduction of response:
	- Proportion of subjects that both CR-PCSS and PR-PCSS scores/ratings are back to their baseline or worse	- Proportion of subjects with both CR-PCSS and PR-PCSS ratings worsening 1-level compared to their corresponding score at Day 71 in the double-blind studies (EN3835-302/303)
	- Proportion of subjects that both CR-PCSS and PR-PCSS scores/ratings are worsening 2- levels comparing to their corresponding score at Day 71 in the double-blind studies (EN3835-302/303)	- Proportion of subjects with both CR-PCSS and PR-PCSS ratings back to their baseline (Day 1 of the double-blind study) or worse
	- Proportion of subjects that either CR-PCSS or PR-PCSS scores/ratings are worsening 2-levels comparing to their corresponding score at Day 71 in the double-blind studies (EN3835-302/303)	- Proportion of subjects with both CR-PCSS and PR-PCSS ratings worsening 2-levels compared to their corresponding score at Day 71 in the double-blind studies (EN3835-302/303)
	- Subjects that both CR-PCSS and PR-PCSS scores/ratings are worsening 1-level comparing to their corresponding score at Day 71 in the double-blind studies (EN3835-302/303)	- Proportion of subjects with either CR-PCSS or PR-PCSS ratings worsening 2-levels compared to their corresponding score at Day 71 in the double-blind studies (EN3835-302/303)
	All results for each endpoint based on the collection time points as scheduled in	All results for each endpoint based on the collection time points as described in

Section	Original Text	Revised Text
	Section 5.1, Section 5.2, and Section 5.3 will be derived and be summarized by treated area , subject category, and study visit (day) using appropriate descriptive statistics.	Section 5.1, Section 5.2, and Section 5.3 will be derived and be summarized by treated area, subject category, and study visit (day) using appropriate descriptive statistics.
Section 17.6 Safety Analyses	Injection site reactions/local tolerability in treated quadrant (through subject and Investigator reporting)	Injection site reactions/local tolerability in treatment area (through subject and Investigator reporting)
	AEs will be summarized by subject category using descriptive statistics. In addition, the safety data will be summarized by treatment period for those re-treated subjects. Descriptive statistics will be presented for each clinical laboratory test for the actual and change from screening at each visit by subject category and vital signs for the actual and change from screening at each visit by subject category.	AEs will be summarized by treatment exposure category, ie, initial exposure to EN3835 in EN3835-302/303 versus re-exposure to EN3835 in this open-label study (EN3835-304) using descriptive statistics.
Section 17.6.4 Vital Signs	Vital sign values are potentially clinically significant (PCS) if they meet both the observed value criteria and the change from baseline criteria. The criteria for PCS vital sign values will be detailed in the Statistical Analysis Plan (SAP).	Vital sign values are potentially clinically important (PCI) if they meet both the observed value criteria and the change from baseline criteria. The criteria for PCI vital sign values will be detailed in the Statistical Analysis Plan (SAP).
Section 17.6.5 Clinical Laboratory Parameters	The number and percentage of subjects with PCS post-baseline clinical laboratory values will be tabulated. The criteria for PCS laboratory values will be detailed in the SAP. A listing of all AEs for subjects with PCS laboratory values will also be provided.	The number and percentage of subjects with PCI post-baseline clinical laboratory values will be tabulated. The criteria for PCI laboratory values will be detailed in the SAP. A listing of all subjects with PCI laboratory values will also be provided.
Section 17.7 Immunogenicity Analyses	Descriptive statistics (percent of positive measurements and average antibody level) will be presented for anti-AUX-I and anti-AUX-II antibody levels at each time point by treated area and by subject category. Average antibody levels will be summarized on logarithmically transposed titer values.	Descriptive statistics (percent of positive measurements and average antibody level) will be presented for anti-AUX-I and anti-AUX-II antibody levels at each time point by treated area and by treatment exposure category. Average antibody levels will be summarized on logarithmically transposed titer values.
	In addition, a subset of subjects with neutralizing anti-AUX-I and anti-AUX-II antibody levels will be summarized by subject category using the binary response (positive/negative).	In addition, a subset of subjects' samples with anti-AUX-I and anti-AUX-II neutralizing antibodies will be summarized using appropriate descriptive statistics.
Section 18.2 Study Drug Packaging and Labeling	Each vial of study drug and diluent will minimally be labeled with contents, Sponsor identification, storage, administration/use, kit number, and appropriate cautions statements	Each vial of study drug and diluent will minimally be labeled with contents, Sponsor identification, storage, administration/use, and appropriate cautions statements; additionally, study drug will be labeled with kit number
Section 18.4 Study Drug Preparation	Dispose of used diluent vials, needles, and syringes per local regulations.	Dispose of used needles and syringes per local regulations.

Section	Original Text	Revised Text
Section 19.1 Source Documents	Added	S-GAIS
Section 21.3 Subject Information and Consent	A unique Subject identification number will be carried over from the double-blind, placebo controlled study (EN3835-302/303).	The unique subject identification number will be carried over from the double-blind, placebo controlled study (EN3835-302/303).

3. SPONSOR CONTACT INFORMATION

Table 1: Sponsor Contact Information

Role in Study	Name	Telephone and Email Address
Clinical Development Lead	[redacted]	Office: [redacted] Cell: Not applicable
Clinical Trial Lead	[redacted]	Office: [redacted] Cell: Not applicable Email: [redacted]
Medical Monitor	[redacted]	Office: Not applicable Cell: [redacted] Email: [redacted]
SAE Reporting Pathway	Not Applicable	FAX: [redacted] Email: [redacted]

A list of other key study personnel and vendors will be provided separately for your reference.

4. SYNOPSIS

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: EN3835

Name of Active Ingredient: Collagenase clostridium histolyticum

Title of Study: A Phase 3b, Open-label, Long-term Study to Evaluate the Safety and Temporal Pattern of Response of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy

Lead Principal Investigator: Not applicable

Study Period:	**Phase of Development**: 3b
Estimated date first subject enrolled: April 2018 Estimated date last subject completed: December 2021	

Primary Objectives:

- To assess the long-term safety of EN3835 in the treatment of edematous fibrosclerotic panniculopathy (EFP) commonly known as cellulite in adult women.
- To assess the safety of EN3835 when used for retreatment in the treatment of EFP commonly known as cellulite in adult women.
- To assess the long-term immunogenicity profile of EN3835 following treatment of EFP commonly known as cellulite in adult women.

Secondary Objectives:

To assess the time to reduction of response (TRR) to EN3835 in the treatment of EFP in adult women.

Study Design:

This open-label extension study will be performed at multiple centers currently participating in the double-blind, placebo-controlled, parent trials (EN3835-302/EN3835-303) in the United States. The open-label extension study will initially enroll up to 840 subjects until the double-blind studies are unblinded, after which only subjects who received active EN3835 will remain in observation in the current study. Subjects who completed the double-blind study and sign an informed consent will be eligible to enter this open-label extension.

Following completion of safety and cellulite assessments (at least Patient Reported Photonumeric Cellulite Severity Scale [PR-PCSS] and the Clinician Reported Photonumeric Cellulite Severity Scale [CR-PCSS]) at Day 71 of the double-blind study (EN3835-302/303), subjects will be asked to continue in the open-label extension to the double-blind study (ie, EN3835-304, the current study). At the time of entry into the open-label study and at Visit 1 at Day 180 of study EN3835-304 (approximately 6 months after Day 71 of study EN3835-302/303), subjects, Investigators and site personnel will remain blinded to study drug treatment received in the double-blind study.

Upon unblinding of the double-blind studies EN3835-302/303 (which may occur immediately after Day 180 Visit assessments are completed if the study drug blind has been broken by Sponsor, or may occur during a visit (Unscheduled Visit) after the Day 180 Visit if the blind is not broken by Sponsor until sometime after Day 180), subjects who received placebo during the double-blind studies will be discontinued, and subjects who received active EN3835 will be classified into one of three categories:

Category I: 1-Level Composite Responders
Category II: 2-Level Composite Responders
Category III: Non-Composite Responders

Category I will include subjects in which the maximum composite response in either (or both) buttock(s) in EN3835-302 or EN3835-303 was ONLY a 1-level composite improvement in cellulite severity as assessed by the PR-PCSS and the CR-PCSS. Category I subjects will be eligible for one additional retreatment course in up to two buttocks in the current open-label study. Retreatment may begin on Day 180 if the study drug blind from the double-blind study (EN3835-302/303) has been

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broken. Only buttocks with a composite 1-level improvement or less will be retreated. Assessment of open-label efficacy following retreatment will be determined up to Treatment Visit 4 (Day 71 + 5 days), after which subjects will be observed for every 6 months for 2 years and then annually for up to 3 years (Day 1080) after Day 71 of study EN3835-302/303. Category II will include subjects who showed an improvement in cellulite severity of at least two levels in at least one buttock in both the PR-PCSS and the CR-PCSS (ie, 2-level composite responder) in EN3835-302 or EN3835-303. These subjects will be observed for TRR (defined below) and safety approximately every 6 months for 2 years and annually for up to 3 years (Day 1080) from Day 71 of the double-blind studies. Category II subjects must have at least a 1-level composite response reduction compared to Day 71 of the EN3835-302/303 study AND no longer maintain a 2-level composite response compared to baseline in the EN3835-302/303 study on either or both buttocks to be eligible for retreatment. Assessment of open-label efficacy following retreatment will be determined up to Treatment Visit 4 (Day 71 + 5 days), after which subjects will be observed for safety every 6 months for 2 years and then annually for up to 3 years (Day 1080) after Day 71 of study EN3835-302/303. Category I and Category II subjects who chose not to be retreated will have cellulite assessments completed during the observational visits at Months 12, 18, 24, and 36. At Months 12, 18, 24, and 36, if the ratings indicate that the buttock(s) is/are eligible for retreatment and the subject has not received EN3835 previously in study EN3835-304, the subject will be offered one course of retreatment for the eligible buttock(s). Category III subjects will include all other subjects who received active EN3835 in study EN3835-302 or EN3835-303 but did not meet criteria to be included in Category I or II (ie, noncomposite responders). These subjects will be observed for safety every 6 months for 2 years and annually for up to 3 years (Day 1080) and will not be eligible for retreatment during the study. The retreatment course for eligible Category I and Category II subjects will consist of 3 treatment sessions separated by 21 days. Each retreatment session will consist of 12 injections (0.07 mg/0.3 mL per injection) of EN3835 for a dose of 0.84 mg and volume of 3.6 mL (identical to the treatment course administered in the double-blind study), in each qualifying buttock in up to two buttocks treated concurrently. One and only one retreatment course in up to 2 qualifying buttocks concurrently will be offered to eligible Category I and Category II subjects during this 3 year study.
Number of Subjects (Planned): Up to approximately 420 active subjects.
Study Center(s): Approximately 50 sites in United States
Diagnosis and Inclusion/Exclusion Criteria: ***All Subjects (Through Day 180)***: Subjects who completed the double-blind Phase 3, study EN3835-302 or EN3835-303, are judged to be in good health, are willing to apply sunscreen to both buttocks before sun exposure, have not received collgenase or any EFP treatments to the buttocks since the completion of study EN3835-302/303, and will not receive other EFP treatments to the buttocks will be eligible to enroll in this period. ***Category I Subjects***: Subjects whose maximum composite response at Day 71 in either or both buttocks in double-blind study EN3835-302 or EN3835-303 was ONLY a 1-level improvement on CR-PCSS/PR-PCSS, are in good health, are willing to apply sunscreen to both buttocks before sun exposure, will not receive other EFP treatments to the buttocks, and have not received any collagenase treatments since the completion of studies EN3835-302/303 were eligible to continue in the study.

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***Category II Subjects**:* Subjects who had a maximum composite response at Day 71 in either or both buttocks in double-blind study EN3835-302 or EN3835-303 was at least a 2-level composite improvement on CR-PCSS/ PR-PCSS, are in good health, are willing to apply sunscreen to both buttocks before sun exposure, will not receive other EFP treatments to the buttocks and have not received any collagenase treatments since the completion of studies EN3835-302/303 are eligible to continue in the study. ***Category III Subjects**:* Received active EN3835 in study EN3835-302 or EN3835-303 but did not meet eligibility criteria for Category I or Category II status are eligible to continue in the study. ***Category I and Category II Subjects Who Opt to Receive Retreatment**:* Category I and Category II subjects who meet all entry criteria outlined above can opt to receive retreatment if they have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to any dose and agree to use an acceptable means of birth control during retreatment. In addition, Category II subjects must have had at least a 1-level composite response reduction compared to Day 71 of the EN3835-302/303 study AND no longer maintain a 2-level composite response compared to baseline in the EN3835-302/303 study on either or both buttocks. Subjects will be excluded from retreatment if they have ineligible systemic disorders, history of local conditions in the area to be treated, require anticoagulant or antiplatelet medications (except ≤150 mg aspirin daily), are nursing (during active retreatment only), intend to use tanning spray or tanning booths in the 30 days prior to or during treatment, or have a known systemic allergy to collagenase.
Investigational Product, Dosage and Mode of Administration: EN3835, up to 1.68 mg, subcutaneous. A dose of 0.84 mg of EN3835 per buttock will be administered as 12 subcutaneous injections (0.3-mL injections administered as three 0.1-mL aliquots per injection) in each qualifying buttock, for a total dose of up to 1.68 mg and a total volume of up to 7.2 mL (3.6 mL per buttock). Total number of injections will be up to 24 injections per treatment visit in up to two buttocks (ie, 12 injections per buttock). For subjects who qualify for retreatment, there will be 3 treatment visits at 21-day intervals, beginning 6 months after Day 71 in their respective double-blind study (EN3835-302/303).
Duration of Study: Up to thirty-six (36) months from Day 71 (approximately 28 days after their last exposure to EN3835) of the study EN3835-302/303.
Criteria for Evaluation: Cellulite assessments (efficacy) will include PR-PCSS, CR-PCSS: Patient Reported Cellulite Impact Scale (PR-CIS) and an abbreviated PR-CIS, Subject Global Aesthetic Improvement Scale (S-GAIS), and Subject Satisfaction with Cellulite Treatment Assessment and Subject Self-Rating Scale (SSRS). Cellulite assessments of PR-PCSS, CR-PCSS and S-GAIS will be performed on each buttock. Each buttock will be evaluated separately. Cellulite assessment of PR-CIS, Subject satisfaction with cellulite treatment assessment, and SSRS will be performed on both buttocks. ***Time to Reduce a 2-Level Composite Response***: For the purposes of this study, a subject treated with EN3835 is considered a 2-level composite responder once an improvement of at least 2 levels on each assessment scale (PR-PCSS/CR-PCSS) is shown at the same visit during the double-blind study at or before Day 71 in either or both buttocks. The time until a reduction of response has occurred is considered to *end* once a subject's cellulite

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severity improvement reduces a composite 1-level, ie, a reduction in severity by 1-level in both the PR-PCSS and CR-PCSS. ***Safety***: Safety will be assessed throughout the study by Adverse events (AEs) (including adverse events of special interest [AESI]), vital signs (at retreatment visits), clinical laboratory tests (prior to retreatment visits and 28 days after the last retreatment dose), immunogenicity assessments (ie, assessed through the determination of binding and neutralizing anti-AUX-I and anti-AUX-II antibody levels). In addition, for subjects treated with study drug in this study, injection site reactions/local tolerability in the treated buttocks (through subject and Investigator reporting) will be assessed.
Statistical Methods: ***Analysis Populations***: Overall Safety Population: All subjects who enter the open-label study period and received EN3835 in study EN3835-302 or EN3835-303. This population will include all Category I, II, and III subjects. All safety analyses will be based on this population. Day-180 Observational Population: All rollover subjects from studies EN3835-302/303. The safety analysis for the data obtained from Screening to Day 180 will be based on this population. TRR: All subjects who have at least 1-level/2-level improvement in both CR-PCSS and PR-PCSS ratings during the double-blind study for either/both treated buttocks. This population will include Category I and II subjects. The TRR data will be collected for up to 3 years for Category I and II subjects. ***Efficacy Analyses:*** The analyses of cellulite assessments will be based on the TRR population. The TRR will be defined from the time of assessing the efficacy (Day 71) in the double-blind study (EN3835-302/303) until the study visit in study EN3835-304 at which a composite 1-level loss of response in both PR-PCSS and CR-PCSS is observed. The defined endpoints will include: • Proportion of subjects with reduction of response - Proportion of subjects with both CR-PCSS and PR-PCSS ratings worsening 1-level compared to their corresponding score at Day 71 in the double-blind study (EN3835-302/303) - Proportion of subjects with both CR-PCSS and PR-PCSS ratings back to their baseline or worse - Proportion of subjects with both CR-PCSS and PR-PCSS ratings worsening 2-levels compared to their corresponding score at Day 71 in the double-blind study (EN3835-302/303) - Proportion of subjects with either CR-PCSS or PR-PCSS ratings worsening 2-levels compared to their corresponding score at Day 71 in the double-blind study (EN3835-302/303) • Proportion of subjects at each level of improvement in the PR-PCSS • Proportion of subjects at each level of improvement in the CR-PCSS • Changes in the PR-CIS total scores from baseline • Proportion of subjects at each level of improvement in the S-GAIS • Proportion of subjects at each level of improvement in the subject satisfaction with cellulite treatment

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- Proportion of subjects at each level of improvement in the SSRS

All results for each endpoint based on the collection time points will be derived and be summarized by treated area, treatment exposure category, and study visit (day) using descriptive statistics.

***Safety Analyses**:*

AEs will be summarized by proportion of subjects reporting each event. Descriptive statistics will be presented for actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter.

***Immunogenicity**:*

Anti-AUX-I and anti-AUX-II antibody levels and a subset of subjects' samples anti-AUX-I and anti-AUX-II neutralizing antibodies will be summarized using descriptive statistics.

5. SCHEDULE OF EVENTS

5.1. Up to 180 Days

Procedures[a]	Screening A[b] (≥Day 71 Visit of Double-blind Study) (+14 days)	Visit 1 Day 180[c] (±14 days) M6/Early Termination	Durability Confirmation Visit[d]
Unblinding of Investigator, subject and site to subjects' treatments in EN3835-302/303[e]		X	
Informed consent[f]	X	X	
Inclusion/exclusion	X		
Digital photography	X	X	X
Prior/concomitant medications/procedures[g]	X	X	
Physical examination:	X		
• Body weight	X	X	
• Height	X		
Vital signs	X	X	
Collection of Samples			
• Clinical laboratory	X	X	
• Anti-AUX-I/anti-AUX-II antibody level	X		
• Pregnancy testing[h]	X	X	
Subject Cellulite Assessments			
• Review assessments' training and use materials	X	X	X
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)[i,j]	X	X	X
• Subject Global Aesthetic Improvement (S-GAIS) [k,l]	X	X	
• Patient Reported Cellulite Impact Scale (PR-CIS) [m,n]	X	X	
• Subject Satisfaction With Cellulite Treatment Assessment[o,p]	X	X	
• Subject Self-Rating Scale (SSRS)	X	X	
Investigator Cellulite Assessments			
• Review assessment's training and use materials	X	X	X
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)[q]	X	X	X
Assignment of Subject to Category I, II, or III[r]		X	
Local safety assessments[s]	X	X	X
Adverse events[t]	Monitored throughout study		

[a] Unscheduled visits may be done as deemed necessary at any time during the study to ensure subject safety; assessments done at unscheduled visits are at the discretion of the investigator. No photographs or cellulite severity assessments will be done at unscheduled visits.
[b] Day 71 Visit in the double-blind study (EN3835-302/303).
[c] Visit 1 Day 180 is in study EN3835-304; approximately 180 days after Day 71 of double-blind study. A subject who terminates study participation between Day 71 and Day 180 will have an Early Termination Visit that includes the Assessments listed for Visit 1 Day 180.
[d] If the composite (CR-PCSS and PR-PCSS) ratings worsen by at least 1-level composite response ratings at the Day 180 Visit or at a subsequent unscheduled unblinding visit for a subject that had a 2-level composite improvement at Day 71 of the double-blind study, an additional visit should be scheduled 14 days (± 5 days) later to confirm reduction of response, via re-assessment with the CR-PCSS and PR-PCSS.
[e] Depending on the date of unblinding of subject's treatment in EN3835-302/303; investigators, subjects, and site personnel may be unblinded at Day 180 Visit AFTER all assessments have been performed or at a time thereafter during an unscheduled visit. If database lock occurs prior to Day 180, the investigator, subjects, and site personnel will remained blinded until the Day 180 Visit.
[f] Informed consent at Screening will address activities up through Day 180 Visit. Informed consent at Day 180 Visit will address the classification of subjects into Categories I, II, and III and activities and assessments that they will undergo.
[g] Including XIAFLEX as a concomitant medication; the use of the word 'prior' refers to the period between the last visit from the previous Phase 3 clinical study through the signing of informed consent in the EN3835-304 study; not applicable to subjects who sign consent for this study on the same day that they complete the EN3835-302/303 study.
[h] Serum pregnancy tests occur during the Screening Visit (carried over from Day 71/EOS visit of EN3835-302/303); urine pregnancy test on Day 180 Visit and, if deemed necessary, at an Unscheduled Visit.
[i] Subject assessments should be completed independently and prior to Investigator assessments at each visit.
[j] Assessment made via photographs.
[q] Assessment of each of the 2 buttocks independently.
[r] Assignment of subjects to Categories will occur after unblinding of investigators, subject and site personnel to subjects' treatment in EN3835-302/303 and will depend on treatment and Day 71 cellulite severity improvements. Depending on the date of the database lock of the double-blind studies, assignments may occur at the Day 180 Visit after assessments are completed or at a time thereafter during an unscheduled visit.
[s] Local adverse events associated with the injection site, including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, peau d'orange changes) cutaneous adverse events, will be recorded and evaluated for seriousness and severity.
[t] Any AE that occurs between the completion of studies EN3835-302/303 and the Day 180 Visit will be reported and evaluated.

EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study; M=Month(s).

5.2. Eligible Category I/II Subjects – Treatment Session Assessments

Procedures[a]	Screening B[b] (Day -14 to -1 relative to Tx Visit 1)	Tx Visit 1 Tx Session 1 Day 1	Tx Visit 2 Tx Session 2 Day 22 (±3 days)	Tx Visit 3 Tx Session 3 Day 43 (±3 days)	Tx Visit 4 End of Treatment Day 71 (+5 days)[c]
Informed consent[d]	X				
Inclusion/exclusion	X				
Digital photography[e]	X	X[f]	X[f]	X[f]	X
Prior/concomitant medications/procedures[g]	X	X	X	X	X
Physical examination:	X				
• Body weight	X		X[h]	X[h]	X
• Height	X				
Vital signs	X	X[i]	X[i]	X[i]	X
ECG[j]	X				
Collection of Samples					
• Clinical laboratory	X				X
• Anti-AUX-I/anti-AUX-II antibody level	X		X	X	X
• Pregnancy testing[k]	X	X[h]	X[h]	X[h]	X
Subject Cellulite Assessments					
• Review assessments' training and use materials	X	X	X	X	X
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)[l,m]	X	X	X	X	X
• Subject Global Aesthetic Improvement Scale (S-GAIS)[l]	X				X
• Patient Reported Cellulite Impact Scale (PR-CIS)[l]	X				X
• Subject Satisfaction With Cellulite Treatment Assessment[l]	X				X
• Subject Self-Rating Scale (SSRS)[l]	X				X
Investigator Cellulite Assessments					
• Review assessment's training and use materials	X	X	X	X	X
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X	X	X	X	X
Selection of dimples to be treated		X	X	X	

Procedures[a]	**Screening B**[b] **(Day -14 to -1 relative to Tx Visit 1)**	**Tx Visit 1 Tx Session 1 Day 1**	**Tx Visit 2 Tx Session 2 Day 22 (±3 days)**	**Tx Visit 3 Tx Session 3 Day 43 (±3 days)**	**Tx Visit 4 End of Treatment Day 71 (+5 days)**[c]
Marking the dimples and injection sites to be treated within the buttocks		X	X	X	
Confirm eligibility of buttocks for retreatment[n]	X				
Study drug administration		X	X	X	
Injection site reactions/local tolerability in the buttocks[o]		X	X	X	X
Adverse events	Monitored throughout study				

[a] Unscheduled visits may be done as deemed necessary at any time during the study to ensure subject safety; assessments done at unscheduled visits are at the discretion of the investigator. No photographs or cellulite severity assessments will be done at unscheduled visits.

[b] After the study drug treatment blind is broken in study EN3835-302/303 and subjects have been classified based on Day 71 composite responses in study EN3835-302/303, Category I and Category II subjects that qualify for treatment may elect to receive one and only one course of EN3835 retreatment (ie, 3 treatment sessions) in up to 2 buttocks. If a subject does not qualify for treatment at that time, she may undergo another Screening B at a later time, if still eligible for treatment.

[c] Upon completion of treatment, subjects will be followed at intervals as described in Section 5.3; if the 71-day treatment period overlaps with an Observation Visit in Section 5.3 for a subject, that particular Observation visit will be skipped and the subject will be assessed at the next scheduled Observation Visit in Section 5.3.

[d] Informed consent for Category I and eligible Category II subjects who opt to receive retreatment.

[e] Photographs of both left and right buttocks should be taken.

[f] Before and after marking dimples and injection sites.

[g] Including XIAFLEX as a concomitant medication; the use of the word 'prior' refers to the period between the last visit from the previous Phase 3 clinical study through the signing of informed consent in the EN3835-304 study; not applicable to subjects who sign consent for this study on the same day that they complete the EN3835-302/303 study.

[h] Before injection.

[i] Up to 4 hours before injection; approximately 15 and 30 minutes after injection. Pulse and blood pressure to be taken after subject has been sitting for 5 minutes. Vital signs must be stable before the subject is discharged. Refer to Section 14.9.

[j] Do not conduct if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-302/303).

[k] Serum pregnancy test occurs at Screening Visit and Day 71/EOS visit; urine pregnancy test on Day 1, Day 22, and Day 43 Visits and Unscheduled Visit.

[l] Assessment made via photographs (if treatment visit, use photographs taken before marking dimples and injection sites).

[m] Subject assessments should be completed independently and prior to investigator assessments at each visit. Includes both buttocks regardless of treatment, each buttock should be assessed independently.

[n] At least one of the Category I subject's buttocks must have scores/ratings of at least 2 in both the CR-PCSS and PR-PCSS to be eligible to receive treatment. Category II subjects must have at least a 1-level composite response reduction compared to Day 71 of the EN3835-302/303 study AND no longer maintain a 2-level composite response compared to baseline in the EN3835-302/303 study on either or both buttocks.

- Local adverse events associated with the injection site, including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, peau d'orange changes) cutaneous adverse events, will be recorded and evaluated for seriousness and severity.

ECG=Electrocardiogram; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study; Tx=Treatment.

5.3. Category I/II Subjects – Observation Assessments

Procedures[a]	OBS Visit 2 Day 360 (±30 d) (M12)	OBS Visit 3 Day 540 (±30 d) (M18)	OBS Visit 4 Day 720 (±30 d) (M24)	OBS Visit 5 Day 1080/EOS/ Early Termination (±30 d) (M36)	Durability Confirmation Visit[b]
Verification of informed consent	X				
Inclusion/exclusion	X				
Digital photography	X	X	X	X	X
Prior/concomitant medications/procedures[c]	X	X	X	X	
Anti-AUX-I/anti-AUX-II antibody level	X	X	X	X	
Subject Cellulite Assessments					
• Review assessments' training and use materials	X	X	X	X	X
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)[d,e]	X	X	X	X	X
• Subject Global Aesthetic Improvement Scale (S-GAIS)[d]	X	X	X	X	
• Patient Reported Cellulite Impact Scale (PR-CIS)[d]	X	X	X	X	
• Subject Satisfaction With Cellulite Treatment Assessment[d]	X	X	X	X	
• Subject Self-Rating Scale (SSRS)	X	X	X	X	
Investigator Cellulite Assessments					
• Review assessment's training and use materials	X	X	X	X	X
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)[e]	X	X	X	X	X
Local safety assessments[f]	X	X	X	X	X
Adverse events	Monitored throughout study				

[a] Unscheduled visits may be done as deemed necessary at any time during the study to ensure subject safety; assessments done at unscheduled visits are at the discretion of the investigator. No photographs or cellulite severity assessments will be done at unscheduled visits.

[b] If the composite (CR-PCSS and PR-PCSS) ratings worsen by at least 1-level composite response ratings for a subject, an additional visit should be scheduled 14 days (± 5 days) later to confirm reduction of response, via re-assessment with the CR-PCSS and PR-PCSS. If reduction of response is confirmed, subjects will be offered one course of retreatment (one and only one course of retreatment in up to 2 buttocks concurrently will be offered to an individual subject during this open-label study from Visit 1 to Visit 5 (approximately 6 to 36 months after Day 71 of the double-blind study, respectively). The Sponsor has decided to terminate the EN3835-304 clinical trial at the completion of 3-year time point (Day 1080) and will offer voucher(s) for commercially approved Qwo redeemable only for those trial participant(s) who will miss their potential retreatment opportunity due to this decision. Retreatment will only be offered following confirmation of eligibility through cellulite assessments performed at the Day 1080 visit for those participants, and a confirmation visit (as applicable).

[c] Including XIAFLEX as a concomitant medication; the use of the word ‘prior’ refers to the period between the last visit from the previous Phase 3 clinical study through the signing of informed consent in the EN3835-304 study; not applicable to subjects who sign consent for this study on the same day that they complete the EN3835-302/303 study.

[d] Assessment made via photographs.

[e] Subject assessments should be completed independently and prior to Investigator assessments at each visit. Assessment of each of the 2 buttocks is to be made independently.

[f] Local adverse events associated with the injection site, including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, peau d’orange changes) cutaneous adverse events, will be recorded and evaluated for seriousness and severity.

d=Days; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study; M=Month(s); OBS=Observation.

5.4. Category III Subjects - Assessments

Procedures[a]	OBS Visit 2 Day 360 (±30 d) (M12)	OBS Visit 3 Day 540 (±30 d) (M18)	OBS Visit 4 Day 720 (±30 d) (M24)	OBS Visit 5 Day 1080 EOS/Early Termination (±30 d) (M36)
Verification of informed consent	X			
Inclusion/exclusion	X			
Prior/concomitant medications/procedures[b]	X	X	X	X
• Anti-AUX-I/anti-AUX-II antibody level	X	X	X	X
Local safety assessments[c]	X	X	X	X
Adverse events	Monitored throughout study			

[a] Unscheduled visits may be done as deemed necessary at any time during the study to ensure subject safety; assessments done at unscheduled visits are at the discretion of the investigator. No photographs or cellulite severity assessments will be done at unscheduled visits.

[b] Including XIAFLEX as a concomitant medication; the use of the word 'prior' refers to the period between the last visit from the previous Phase 3 clinical study through the signing of informed consent in the EN3835-304 study; not applicable to subjects who sign consent for this study on the same day that they complete the EN3835-302/303 study.

[c] Local adverse events associated with the injection site from the 302/303 studies, including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, peau d'orange changes) cutaneous adverse events, will be recorded and evaluated for seriousness and severity.

d=Days; EOS=End of study; M=Month; OBS=Observation

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7. LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Table 2: Abbreviations

Abbreviation	Definition
AE	Adverse event
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
CR-PCSS	Clinician Reported Photonumeric Cellulite Severity Scale
CSS	Cellulite severity scale
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EFP	Edematous fibrosclerotic panniculopathy
ePRO	Electronic patient reported outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
I-GAIS	Investigator Global Aesthetic Improvement Scale
IRB	Institutional Review Board
IWRS	Interactive web response system
PR-CIS	Patient Reported Cellulite Impact Scale
PR-PCSS	Patient Reported Photonumeric Cellulite Severity Scale
SAE	Serious adverse event
S-GAIS	Subject Global Aesthetic Improvement Scale
SSRS	Subject Self-Rating Scale
TEAE	Treatment-emergent adverse event
TRR	Time to reduction of response

8. INTRODUCTION

8.1. Background

8.1.1. Edematous Fibrosclerotic Panniculopathy

Edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, has been defined as a local metabolic disorder of subcutaneous tissues that results in a contour abnormality of the skin.(1) The condition manifests as dimpled skin, particularly in the gluteal-femoral region.(2,3) EFP is caused by herniation of subcutaneous fat lobules through the dermohypodermal junction and/or shortening of the collagen septa that cross the hypodermal layer and connects the dermis to the underlying fascia. This creates an uneven surface with dimpling.(1,2) EFP is a medical condition resulting in a potentially cosmetically unacceptable alteration of the skin, and affects an estimated 85% to 98% of postpubertal women.(1,3)

The pathophysiology of EFP is not completely understood, but there are 3 main theories: edema resulting from excessive hydrophilia of the intercellular matrix, alteration of the regional microcirculation, and different anatomical conformation of collagenous subcutaneous tissues in women versus men.(4)

It is known that EFP is different from generalized obesity. In generalized obesity, adipocytes undergo hypertrophy and hyperplasia that are not limited to the pelvis, thighs, and abdomen.(1) In areas of EFP, adipocytes have physiologic and biochemical properties that differ from adipose tissue located elsewhere. Large, metabolically-stable adipocytes characterize EFP-prone areas; thus, the responsiveness to catecholamine-induced lipolysis is less in EFP tissues compared to visceral fat, which has the greatest responsiveness.(1)

Subcutaneous fat lobes are separated from one another by thin, usually rigid strands of collagenous connective tissues, which cross the fatty layers and connect the dermis to the underlying fascia. These septa stabilize the subcutis and divide the fat. In EFP, shortening of the collagen septa due to fibrosis provokes retraction at the insertion points of the trabeculae, causing the depressions that characterize EFP.(2) There are a higher percentage of thinner, perpendicular hypodermal septa in women with EFP than in men.(1) Weight gain makes EFP more noticeable, but it may be present even in thin subjects. Genetics may also play a role since EFP tends to run in families.

8.1.2. Current EFP Treatments

There are therapies that have been utilized in an attempt to treat cellulite; however, there are no approved pharmacologic treatments. Despite multiple therapeutic modalities, there is little scientific evidence that any of these treatments are beneficial. In fact, much of the evidence is anecdotal, subjective, or based only on patient self-assessment.(5) Some of the historical treatments for EFP have included weight loss,(6) topical agents,(5) massage,(7) liposuction,(5,6) mesotherapy,(6) radiofrequency,(6) subcision and powered subcision,(8) and laser therapies;(9,10) some of these treatments may pose an increased risk for adverse effects.(5)

There remains an unmet medical need for safe and effective therapies to improve the aesthetic outcome in women with cellulite. To effectively treat cellulite, a therapeutic approach may require disruption of the dermal septa, which are composed of collagen and cause the skin dimpling that is bothersome to many women.

8.1.3. EN3835 (Collagenase Clostridium Histolyticum)

Endo Pharmaceuticals Inc. (Endo) is developing EN3835 for the treatment of EFP. Because EN3835 is a proteinase that can hydrolyze the triple-helical region of collagen under physiological conditions, EN3835 has the potential to be effective in lysing subdermal collagen, such as those observed in the dermal septa, which are the underlying cause of the skin dimpling in women with EFP. EN3835 targets the collagenase structural matrix (eg, dermal septa) at the site of injection and does not require systemic exposure to be effective.

EN3835 is a parenteral lyophilized product comprised of 2 collagenases in an approximate 1:1 mass ratio, Collagenase I (AUX-I, Clostridial class I collagenase) and Collagenase II (AUX-II; Clostridial class II collagenase). These collagenases are isolated and purified from the fermentation of *Clostridium histolyticum*.

Collagenase AUX-I is a single polypeptide chain containing approximately 1,000 amino acids of known sequence and with a molecular weight of 114 kDa. Collagenase AUX-II is also approximately 1,000 amino acids long and has a molecular weight of 113 kDa. These 2 collagenases are not immunologically cross-reactive and have different specificities, such that together they become synergistic, providing a very broad hydrolyzing reactivity toward collagen. Clostridial collagenases are proteinases that can hydrolyze the triple-helical region of collagen under physiological conditions.

EN3835 is currently approved (brand name is XIAFLEX®) for: 1) the treatment of adults with Dupuytren's contracture with a palpable cord and, 2) for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30° at the start of therapy.

A recent Phase 2b, randomized, double-blind, placebo-controlled study (EN3835-201) of 375 women randomized to treatment of one treatment area (quadrant) (quadrant was defined in study EN3835-201 as a left buttock, a right buttock, a left posterolateral thigh or a right posterolateral thigh) of cellulite with EN3835 0.84 mg or placebo in a 1:1 ratio assessed the effectiveness and safety of EN3835. Efficacy in this study was evaluated based on cellulite assessments using Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS), Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS), Investigator Global Aesthetic Improvement Scale (GAIS-I), Subject Global Aesthetic Improvement Scale (GAIS-S), and Subject Satisfaction with Cellulite Treatment.

Results from the Phase 2b study demonstrated that treatment (3 visits approximately 21 days apart) improved the cellulite severity of the treatment area as assessed by the primary endpoint of 2-level composite responder analyses, the proportion of responders based on an improvement of ≥2 levels in the appearance of cellulite in both the patient PR-PCSS and the clinician CR-PCSS of buttocks and thighs was statistically significantly greater in subjects who received EN3835 0.84 mg (10.6%; $p<0.001$) compared to subjects who received placebo (1.6%); 1-level (or greater) responders in the PR-PCSS of EN3835-treated subjects (72.3%) was significantly

greater than 1-level responders in the placebo group (51.6%) ($p<0.001$); statistically significant ($p\leq0.001$) improvement in the appearance of cellulite based on the subject S-GAIS were observed in EN3835 0.84-mg group (73.1%) compared to the placebo group (44.0%); and 62.9% of subjects in the EN3835 0.84 mg group were satisfied or very satisfied with the results of their cellulite treatment compared with only 35.9% of subjects in the placebo group ($p<0.001$). In subjects treated in buttocks (n=187), the proportion of 2-level composite responders was statistically significantly greater in subjects who received EN3835 0.84 mg (14.9%; $p<0.001$) compared to subjects who received placebo (1.1%); 1-level (or greater) responders in the PR-PCSS of EN3835-treated subjects (72.7%) was significantly greater than 1-level responders in the placebo group (47.8%) ($p<0.001$).

The study also demonstrated EN3835 to be well tolerated with no serious adverse events (SAEs) related to EN3835. Safety results from a total of 4 studies (1 pilot, 2 Phase 1, and 2 Phase 2 studies) in which 435 adult females received subcutaneous injections of EN3835 indicate that the majority of treatment-emergent adverse events (TEAEs) are transient, non-serious, mild or moderate in intensity, and related to the local administration of EN3835. The immunogenicity profile after 3 treatment visits of EN3835 indicate that greater than 90% of EN3835-treated subjects were seropositive for AUX-I and/or AUX-II antibodies; this profile of EN3835 is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.

A Phase 1, open-label safety and pharmacokinetic study of a single dose of EN3835 0.84 mg in 11 female subjects with EFP showed that there was no quantifiable levels of AUX-I or AUX-II at any time point after subcutaneous injection of EN3835 0.84 mg into one quadrant. A second Phase 1, open-label safety and pharmacokinetic study of a single dose of EN3835 0.84 mg per treatment area in two treatment areas (buttock-buttock, thigh-thigh, or buttock-thigh) concurrently (total dose of 1.68 mg) showed that there was no quantifiable levels of AUX-I or AUX-II at any time point post- injection of EN3835 1.68 mg.

The results from these studies suggest that subcutaneous injections of EN3835 in the area of cellulite may be a well-tolerated and effective medical treatment for adults with EFP.

8.2. Summary of Nonclinical Studies

Non-clinical studies necessary to support clinical studies have been performed and are summarized in the Investigator Brochure (IB).(11) Non-clinical studies in the following areas were performed: toxicology, reprotoxicity, genotoxicity, and hypersensitivity.

8.3. Summary of Known Risks and Benefits

A summary of safety risks is provided in the IB.(11) The following events have been commonly observed: local injection site reactions (injection site bruising, injection site swelling, and injection site pain) for the various approved indications as well as those being investigated. In the phase 2b study of EN3835 in women with EFP, the following treatment related adverse events ≥2% of 189 EN3835-treated women were reported: injection site bruising (75.1%), injection site pain (59.3%), injection site nodule (14.3%), injection site pruritus (11.1%), injection site swelling (7.4%), injection site induration (5.8%), injection site mass (5.3%), injection site discoloration (3.2%), and injection site erythema (2.1%). These events are similar to events reported in the clinical trials of EN3835 for the approved indications. Postmarketing safety data are consistent with safety data reported in clinical trials.

Although a thorough benefit of EN3835 has not been fully evaluated in the treatment of EFP, the efficacy results from the Phase 2b study and previous EFP studies warranted further development. For a comprehensive review of relevant safety information, please refer to the Investigator Brochure.

8.4. Rationale

The results from the Phase 2b EFP study (EN3835-201) further suggested that EN3835 0.84 mg per treatment area (quadrant) is an effective treatment of EFP based on improvement in the severity of cellulite as determined by the Investigator and the subject. There were no safety concerns following 0.84 mg per treatment area in the treatment of EFP (Section 8.1.3). Safety findings from the Phase 2b EFP study are similar to that observed in previous clinical studies with EN3835 in the treatment of EFP and XIAFLEX in the treatment of Dupuytren's contracture and Peyronie's disease, in that that the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment. The immunogenicity profile of EN3835 in the Phase 2b EFP study is similar in previous studies and programs.

Based on the efficacy and safety findings from the Phase 2a and 2b EFP studies, the EN3835 0.84-mg dose per treatment area in two treatment areas (buttocks) warranted further investigation of the use of EN3835 in the treatment of EFP.

Studies EN3835-302 and EN3835-303 are both phase 3, double-blind, placebo-controlled, multi-center studies designed to assess the safety and efficacy of EN3835 for the treatment of EFP in the buttocks. In each study, eligible subjects will have both buttocks treated with EN3835 or placebo, and will be assessed for cellulite severity for 71 days. After subjects complete the double-blind study, subjects who received active EN3835 in the double-blind studies will roll over into the current long-term study for continued safety assessments (including immunogenicity profile) and efficacy assessments where applicable for up to 3 years. In addition, subjects who showed only a 1-level composite improvement in cellulite severity in the double-blind studies will be eligible for an additional open-label treatment course in the open-label study. The retreatment course for eligible subjects will follow the same regimen as previous studies, utilizing 0.84 mg per treatment area.

9. OBJECTIVES

9.1. Primary Objective

The primary objectives of this study are to assess:

- the long-term safety of EN3835 in the treatment of edematous fibrosclerotic panniculopathy (EFP) commonly known as cellulite in adult women
- the safety of EN3835 when used for retreatment in the treatment of EFP commonly known as cellulite in adult women
- the long-term immunogenicity profile of EN3835 following treatment of EFP commonly known as cellulite in adult women

9.2. Secondary Objectives

The secondary objective of this study is to assess the time to reduction of response (TRR) to EN3835 in the treatment of EFP in adult women.

9.3. Exploratory Objectives

There are no exploratory objectives of this study.

10. INVESTIGATIONAL PLAN

10.1. Study Design

This open-label extension study will be performed at multiple centers currently participating in the double-blind, placebo-controlled, parent trials (EN3835-302/EN3835-303) in the United States. The open-label extension study will initially enroll up to 840 subjects until the double-blind studies are unblinded, after which only subjects who received active EN3835 will remain in observation in the current study. Subjects who completed the double-blind study and sign an informed consent will be eligible to enter this open-label extension.

Following completion of safety and cellulite assessments (at least Patient Reported Photonumeric Cellulite Severity Scale [PR-PCSS] and the Clinician Reported Photonumeric Cellulite Severity Scale [CR-PCSS]) at Day 71 of the double-blind study (EN3835-302/303), subjects will be asked to continue in the open-label extension to the double-blind study (ie, EN3835-304, the current study). Assessments made at Day 71/EOS of the double-blind study will serve as initial screening for the current open-label extension study. At the time of entry into the open-label study and at Visit 1 at Day 180 of study EN3835-304 (approximately 6 months after Day 71 of study EN3835-302/303), subjects and Investigators and site personnel will remain blinded to study drug treatment received in the double-blind study. Even if the EN3835-302/303 study drug blind is broken by the Sponsor; subjects, Investigators and site personnel in study EN3835-304 will remain blinded until after Day 180 safety and cellulite severity assessments of each treatment area are completed. Upon completion and unblinding of the double-blind studies EN3835-302/303 (which may occur immediately after Day 180 Visit assessments are completed if the study drug blind has been broken by Sponsor, or may occur during a visit (Unscheduled Visit) after the Day 180 Visit if the blind is not broken by Sponsor until sometime after Day 180), subjects who received placebo during the double-blind studies will be discontinued, and subjects who received active EN3835 will be classified into one of three categories:

Category I: 1-Level Composite Responders

Category II: 2-Level Composite Responders

Category III: Non-Composite Responders

Category I will include subjects in which the maximum composite response in either (or both) buttock(s) in EN3835-302 or EN3835-303 was ONLY a 1-level composite improvement in cellulite severity as assessed by the PR-PCSS and the CR-PCSS. In cases where there is an improvement in both buttocks, the composite improvement of one level must have occurred in the same buttock to be eligible (ie, the PR-PCSS and CR-PCSS improvement must have been in the same buttock). Subjects showing a 2-level improvement in one scale but only a 1-level improvement in the other scale are also considered Category I subjects, provided the composite improvement is within the same buttock. Category I subjects will be eligible for one additional retreatment course in up to two buttocks in the current open-label study. Retreatment may begin on Day 180 if the study drug blind from the double-blind study (EN3835-302/303) has been broken. Only buttocks with a composite 1-level improvement or less will be retreated. Assessment of open-label efficacy following retreatment will be determined up to Treatment Visit 4 (Day 71 + 5 days), after which subjects will be observed, depending when during the 3-year period the subject receives retreatment, every 6 months for 2 years and then annually for

up to 3 years (Day 1080) after Day 71 of study EN3835-302/303. Eligible subjects who qualify for Category I status who choose NOT to receive additional retreatment will have observation visits (Visits 2-5) as detailed in Section 5.3.

Category II will include subjects who showed an improvement in cellulite severity of at least 2 levels in at least one buttock in both the PR-PCSS and the CR-PCSS (ie, 2-level composite responder) in EN3835-302 or EN3835-303. These subjects will be observed for TRR (defined below) and safety approximately every 6 months for 2 years and will be observed annually for up to 3 years (Day 1080) from Day 71 of the double-blind studies. Category II subjects must have at least a 1-level composite response reduction compared to Day 71 of the EN3835-302/303 study AND no longer maintain a 2-level composite response compared to baseline in the EN3835-302/303 study on either or both buttocks to be eligible for retreatment as detailed in Section 5.2; after which they will be observed at observation visits as detailed in Section 5.3.

Category I and Category II subjects who participate in the observational phase of the study, will have cellulite assessments completed during the observational visits at Months 12, 18, 24, and 36. At Months 12, 18, 24, and 36, if the ratings indicate that the buttock(s) is eligible for retreatments and the subject has not received EN3835 previously in study EN3835-304, the subject will be offered one course of treatment for the eligible buttock(s); one course of concurrent treatment for up to two eligible buttocks.

Category III subjects will include all other subjects who received active EN3835 in study EN3835-302 or EN3835-303 but did not meet criteria to be included in Category I or II (ie, noncomposite responders). These subjects will be observed for safety every 6 months for 2 years and annually for up to 3 years (Day 1080) as detailed in Section 5.4, and will not be eligible for retreatment during the study.

The retreatment course for eligible Category I and Category II subjects will consist of 3 treatment sessions separated by 21 days. Each retreatment session will consist of 12 injections (0.07 mg/0.3 mL per injection) of EN3835 for a dose of 0.84 mg and volume of 3.6 mL (identical to the treatment course administered in the double-blind study), in each qualifying buttock (Table 3) in up to two buttocks treated concurrently. One and only one retreatment course in up to 2 qualifying buttocks concurrently will be offered to eligible Category I and Category II subjects during this 3 year study. After initiation of retreatment (on Treatment Visit 1; Treatment Day 1), subjects will be assessed for safety on each day of injection during retreatment, and assessed for safety and cellulite severity on Treatment Visit 2 (Day 22), Treatment Visit 3 (Day 43) and Treatment Visit 4 (Day 71).

For study purposes; reduction of response (ie, lessening of response or loss of response) is defined as a 1-level composite worsening of cellulite severity improvement observed at Day 71 of the double-blind studies (EN3835-302/303) on both the PR-PCSS and CR-PCSS. TRR is defined as the time from assessing efficacy (Day 71 of double-blind study) to the study visit at which a composite 1-level loss of response in both PR-PCSS and CR-PCSS is observed. Durability of response is defined as a complete loss of response in which cellulite severity returns back to baseline levels (on both the PR-PCSS and CR-PCSS on Day 1 of the double-blind studies). Confirmation of reduction of response and/or complete loss of response will be established during a follow-up visit ~2 weeks after a composite reduction of response is first detected.

Once enrolled in the current open-label study, subjects will again receive instructions for use of the PR-PCSS and will subsequently use the scale to rate the severity of their cellulite in each of the treatment areas on a standardized computer monitor with the PR-PCSS instrument. This independent self-assessment will take place in a private setting to minimize any potential bias from site personnel. The Investigator will then assess the subject's treatment areas live in real-time using the CR-PCSS. Both the Investigator and the subject will remain blinded to each other's assessments for the duration of the open-label study, even after the study drug treatment blind is broken for each double-blind study by the Sponsor. Throughout the study, subjects and Investigators will be provided training materials and will refresh on training prior to the use of each cellulite assessment at each visit.

The Schedule of Events for all subjects up through 180 days following studies EN3835-302/303 is provided in Section 5.1. Beyond Day 180, the Schedule of Events for subjects classified as categories I and II and who are eligible and opt to receive retreatment is provided in Section 5.2 and in observational phase of study Section 5.3. The Schedule of Events for subjects in Category I or Category II who are not eligible for retreatment, or are in Category I and II and who are eligible but opt not to have retreatment, is provided in Section 5.3. The Schedule of Events for Category III subjects is shown in Section 5.4.

Figure 1: Study Design

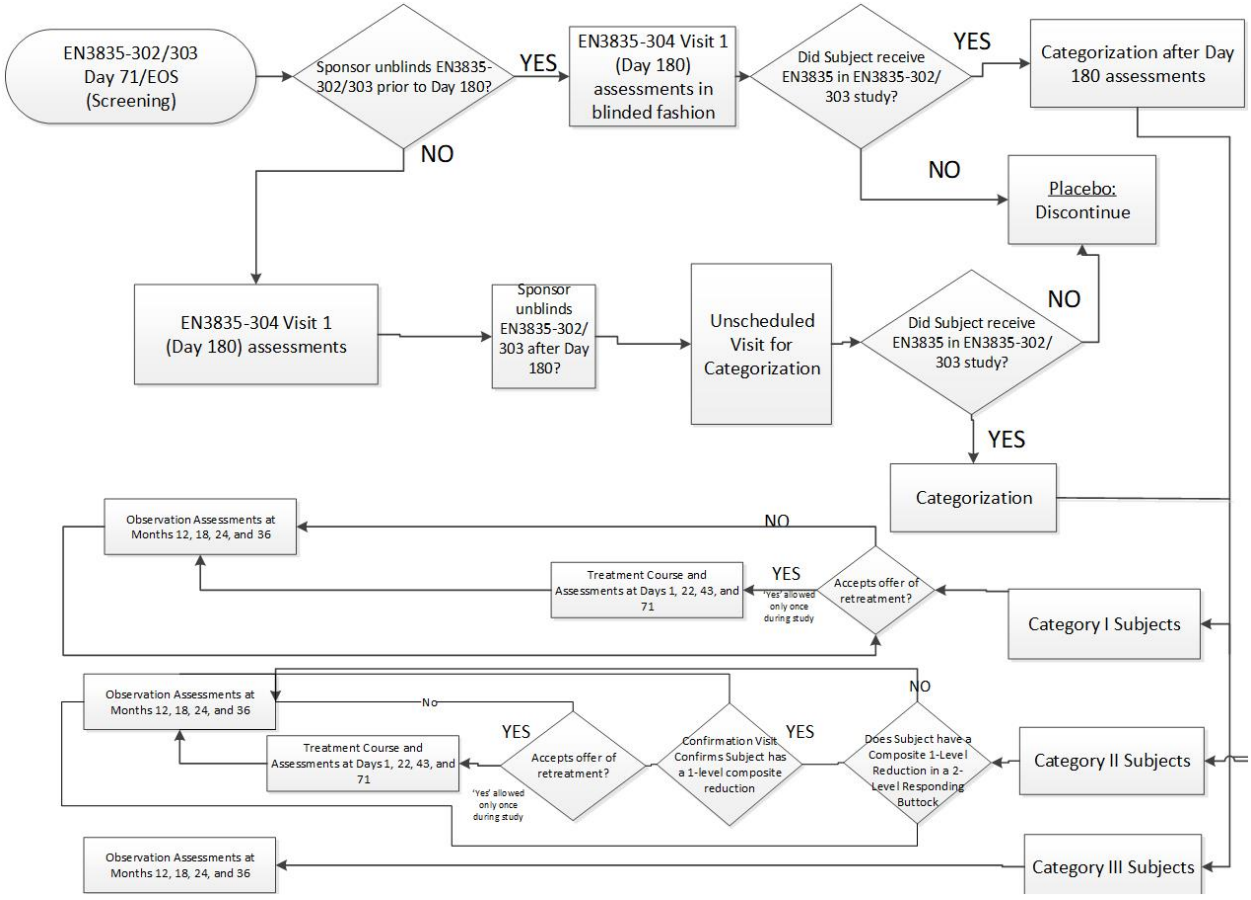


Table 3: Study Retreatment (Eligible Category I and Category II Subjects Only)

Dose per Each Injection [a]	Injection Volume per Each Injection	Number of Injections at Each Treatment Visit	Dose (mg) at Each Treatment Visit	Injection Volume (mL) per Each Treatment Visit	Cumulative EFP Dose
EN3835 0.07 mg	0.3 mL	12 per buttock × up to 2 buttocks = up to 24 injections	0.84 mg per buttock × up to 2 buttocks = 1.68 mg (12 injections per buttock × 0.07 mg/injection × up to 2 buttocks)	3.6 mL per buttock × up to 2 buttocks = up to 7.2 mL (24 injections × 0.3 mL)	5.04 mg (3 treatment visits × 0.84 mg per buttock × up to 2 buttocks)

[a] Each injection of study drug is 0.3 mL administered as three 0.1 mL aliquots.

10.2. Selection of Doses

Based on the efficacy and safety findings from the Phase 2a and 2b EFP studies, the EN3835 0.84-mg dose per treatment area was carried forward to the parent double-blind studies EN3835-302/303, and to this open-label extension study in subjects getting retreatment. The findings from previous studies that the majority of adverse events (AEs) after EN3835 treatment are local to the injection site and that there is no quantifiable systemic exposure observed after concurrent treatment of two buttocks (0.84 mg/buttock; total dose of 1.68 mg) supports the proposed dose to evaluate EN3835 in treatment of one or both buttocks.

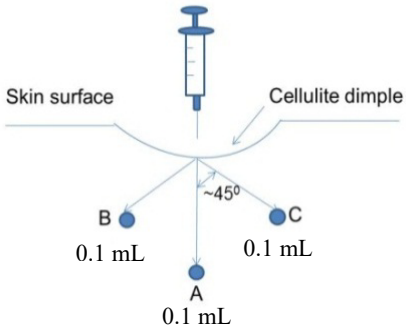
For a complete history of prior investigations related to the selection of dose used in the current study, refer to the IB.(11)

10.3. Study Drug Administration (Eligible Category I and Category II Subjects)

Study drug will be injected subcutaneously while the subject is in a prone position using a syringe with a 30-gauge ½-inch needle. Each injection site will receive a single skin injection of study drug administered as three 0.1-mL aliquots to Positions A, B, and C (for a total injection volume of 0.3 mL) as shown in Figure 2. The depth of injection corresponds to the length of the treatment needle (0.5 inches) from the tip of the needle to the hub or base of the needle without downward pressure.

During each retreatment visit, 4 syringes per buttock will be prepared for dosing. Each syringe will contain 0.9 mL of study drug (ie, 3 injections in each syringe). Twelve (12) skin injections of 0.3 mL per injection will be administered within each buttock getting retreated during each treatment visit.

Figure 2: Study Drug Administration at Each Injection Site



- **Needle Tip Position A**: Position the needle at 90° angle perpendicular to the skin surface at the injection site and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.
- **Needle Tip Position B**: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (but not more than 45°) off vertical and above the long axis of the dimple and inject one 0.1-mL aliquot of study drug) by gently pushing on the syringe plunger. Position B should be towards the head (cephalad) of the subject.
- **Needle Tip Position C**: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (but not more than 45°) off vertical and below the long axis of the dimple and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger. Position C should be towards the feet (caudal) of the subject.
- Withdraw needle from the skin completely and move to the next identified injection site. Complete a total of three 0.3-mL injections (each administered as three 0.1 mL aliquots) and discard the first syringe appropriately. Use the second, third and fourth syringes to complete dosing in each buttock (three 0.3-mL injections per syringe, each injection administered as three 0.1-mL aliquots). Twelve (12) skin injections of 0.3 mL will be administered within each of the two treated buttocks during each treatment visit.
- The plane containing injection deposition points A, B, and C should be perpendicular to the skin and perpendicular to the long axis of a dimple if the dimple is an elongated trough-like dimple. In most cases, the plane containing injection points A, B, and C will be parallel to the long axis of the subject's body.
- After treatment the subject will remain prone for at least 5 minutes.

The total number of dimples treated and the total number of injections administered will be recorded during Treatment Visits 1, 2, and 3.

NOTE: EN3835 is a foreign protein and Investigators must be prepared to address and manage an allergic reaction should it occur. At the time of each injection, a 1:1,000 solution of epinephrine for injection, 50-mg diphenhydramine injection or a suitable equivalent, and oxygen must be available, and the Investigator and site staff must be familiar with their use.

10.4. Care Procedures After Injection

To evaluate the subject for possible immediate immunological AEs, the subject will remain in direct observation of medical personnel who are skilled in the management of an allergic reaction for 30 minutes after receiving the injections of study drug and until the subject exhibits no sign of an immunological or other clinically significant systemic or local AE. The subject's vital signs should be stable before the subject can leave direct observation (see Section 14.9).

The Investigator or qualified designee will then apply a sterile dressing to the injection areas with hypoallergenic tape. The subject will be instructed to remove the dressing in the evening.

10.5. Discussion of Study Design, Including the Choice of Control Groups

This study is a long-term follow-up study of subjects who received EN3835 0.84 mg per buttock in the concurrent treatment (total dose of up to 1.68 mg) of 2 bilateral buttocks with EFP in adult women in a 71-day double-blind, placebo-controlled study (EN3835-302 or EN3835-303). After completion in one of the aforementioned studies, subjects will be followed for up to 3 years from the Day 71 of the double-blind study (EN3835-302/303), which is approximately 28 days after the last exposure of EN3835 in study EN3835-302/303. Study EN3835-304 is being conducted as a multi-center, open-label extension study. The use of the open-label extension design allows for the following:

- Safety data over the course of up to 3 years (1080 days following Day 71 of double-blind) will be collected to assist in further defining the safety profile of EN3835 in this population,
- Safety data, immunogenicity, and responsiveness after repeat exposure (retreatment) and monitoring of previously EN3835 treated subjects for up to 3 years (1080 days following Day 71 of double-blind),
- Safety data, immunogenicity and responsiveness after repeat exposure (retreatment) in subjects that show a reduction from the improvement observed at Day 71 of the double-blind studies and
- Time to reduction in the response to EN3835 using cellulite severity assessments will be evaluated at various time points.

11. SELECTION AND WITHDRAWAL OF SUBJECTS

11.1. Subject Inclusion Criteria

11.1.1. Inclusion Criteria - All Subjects (Through Day 180)

In order to be eligible to participate in the study, subjects must:

1. Voluntarily sign and date an informed consent agreement.
2. Have participated in and completed the double-blind Phase 3 study EN3835-302 or EN3835 303 (ie, assessed safety and obtained PR-PCSS and CR-PCSS ratings at Day 71/EOS of the double-blind study; does not include early termination subjects).
3. Be willing to apply sunscreen to both buttocks before each exposure to the sun and/or tanning booths while participating in the study during this period.
4. Be judged to be in good health, based upon the results of a physical examination and laboratory profile at Screening.
5. Be willing and able to cooperate with the requirements of the study.
6. Be able to read, complete and understand the patient reported outcomes rating instruments in English.

NOTE: After Day 180 Visit assessments are completed in study EN3835-304 and unblinding of EN3835-302/303, subjects who received EN3835 in EN3835-302 or EN3835-303 will be placed into one of three categories based on their responder status of each of their buttocks at Day 71 in study EN3835-302 or EN3835-303 (Section 10.1). Investigators, subjects and all site personnel will be blinded to the treatment that the subjects received in the double-blind studies until assessments at the Day 180 visit of study EN3835-304 are completed; even if this visit occurs after the EN3835-302/303 studies are unblinded by Endo. Investigator, subjects, and site personnel will be unblinded on Day 180 of study EN3835-304 after Day 180 assessments are completed or at an Unscheduled Visit, pending when database lock and unblinding of studies EN3835-302/303 occurs relative to Day 180 of this current study EN3835-304. The following additional inclusion criteria will apply after Day 180 to subjects in Categories I, II, and III as well as to subjects in Categories I and II who opt to be retreated.

11.1.2. Inclusion Criteria - Category I Subjects (Post Unblinding of EN3835-302/303)

In order for Category I subjects to continue to participate in this study, subjects must:

1. Voluntarily sign and date an informed consent agreement.
2. Have received active EN3835 in study EN3835-302 or EN3835-303.
3. Have had a maximum composite response at Day 71 in either or both buttocks in double-blind study EN3835-302 or EN3835-303 that was ONLY a 1-level improvement on CR-PCSS/PR-PCSS.
4. Be willing to apply sunscreen to the buttocks before each exposure to the sun.
5. Be judged to be in good health, based upon the results of a physical examination and laboratory profile at Screening.

6. Be willing and able to cooperate with the requirements of the study.
7. Be able to read, complete and understand the patient reported outcomes rating instruments in English.

11.1.3. Inclusion Criteria - Category II Subjects (Post Unblinding of EN3835-302/303)

In order for Category II subjects to continue to participate in this study, subjects must:

1. Voluntarily sign and date an informed consent agreement.
2. Have received active EN3835 in study EN3835-302 or EN3835-303.
3. Have had a composite response at Day 71 in either or both buttocks in double-blind study EN3835-302 or EN3835-303 that was at least a 2-level composite improvement on CR-PCSS/ PR-PCSS.
4. Be willing to apply sunscreen to the buttocks before each exposure to the sun.
5. Be judged to be in good health, based upon the results of a physical examination, and laboratory profile at Screening.
6. Be willing and able to cooperate with the requirements of the study
7. Be able to read, complete and understand the patient reported outcomes rating instruments in English

11.1.4. Inclusion Criteria - Category III Subjects (Post Unblinding of EN3835-302/303)

In order for Category III subjects to participate in this study, subjects must:

1. Voluntarily sign and date an informed consent agreement.
2. Have received active EN3835 in study EN3835-302 or EN3835-303 but did not meet eligibility criteria for Category I or Category II status.
3. Be willing and able to cooperate with the requirements of the study.

11.1.5. Inclusion Criteria - Category I and Category II Subjects Who Opt for Retreatment (Post Unblinding of EN3835-302/303)

Subjects in Category I and Category II who opt for retreatment must meet the following additional inclusion criteria to be eligible for retreatment. These subjects must:

1. Voluntarily sign and date an informed consent agreement for retreatment.
2. Be willing to apply sunscreen to the buttocks before each exposure to the sun while participating in the retreatment portion of the study (ie, Treatment Visit 1 through Treatment Visit 4).
3. Be judged to be in good health, based upon the results of a physical examination, and laboratory profile at Screening.
4. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test before injection of study drug and be using a stable and effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment and for

the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile.

5. Category II subjects must have at least a 1-level composite response reduction compared to Day 71 of the EN3835-302/303 study AND no longer maintain a 2-level composite response compared to baseline in the EN3835-302/303 study on either or both buttocks that is confirmed at a Confirmation Visit.

11.2. Subject Exclusion Criteria

11.2.1. Exclusion Criteria - All Subjects (Through Day 180)

For the period from completing Day 71 of the double-blind study (EN3835-302 or EN3835-303) through Day 180 (Visit 1) of study EN3835-304, in order to be eligible to participate in the study, subjects must meet the following exclusion criteria.

A subject will be excluded from study participation if she:

1. Intends to or has used any of the following for the treatment of EFP on a buttock at any time during the time period from Day 71 of double-blind study EN3835-302 or EN3835-303 through Day 180 Visit in study EN3835-304 (approximately 6 months after Day 71 of study EN3835-302 or EN3835-303), including (but not limited to):
    a. Liposuction in a buttock
    b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock
    c. Any investigational drug or treatment for EFP on a buttock (other than treatment in study EN3835-302/303)
    d. Endermologie or similar treatments within a buttock
    e. Massage therapy within a buttock during the 3-month period before observational visit
    f. Creams (eg, Celluvera, TriLastin) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before observational visit
2. Intends to use tanning spray or tanning booths during this period.
3. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study.

NOTE: After Day 180 Visit assessments are completed in study EN3835-304 and unblinding of EN3835-302/303, subjects who received EN3835 in EN3835-302 or EN3835-303 will be placed into one of three categories based on their responder status of each of their buttocks at Day 71 in study EN3835-302 or EN3835-303 (Section 10.1). Investigators, subjects and all site personnel will be blinded to the treatment that the subjects received in the double-blind studies until assessments at the Day 180 visit of study EN3835-304 are completed; even if this visit occurs after the EN3835-302/303 studies are unblinded by Endo. Investigator, subjects and site personnel will be unblinded on Day 180 of study EN3835-304 after Day 180 assessments are completed or at an Unscheduled Visit, pending when database lock and unblinding of studies

EN3835-302/303 occurs relative to Day 180 of this current study EN3835-304. The following additional exclusion criteria will apply after Day 180 to subjects in Categories I, II, and II as well as to subjects in Categories I and II who opt to be retreated.

11.2.2. Exclusion Criteria - Category I and Category II Subjects (Post Unblinding of EN3835-302/303)

A Category I or Category II subject will be excluded from study participation if she:

1. Intends to or has used any of the following for the treatment of EFP on a buttock at any time during the course of the study:
    a. Liposuction in a buttock.
    b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock.
    c. Any investigational drug or treatment for EFP on a buttock (other than treatment in study EN3835-302/303).
    d. Endermologie or similar treatments within a buttock.
    e. Massage therapy within a buttock during the 3-month period before observational visit.
    f. Creams (eg, Celluvera, TriLastin) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before observational visit.
2. Has received any collagenase treatments at any time since completion of the double-blind study
3. Any other condition(s) that, in the Investigator's opinion, might indicate that the subject is unsuitable for the study.

11.2.3. Exclusion Criteria - Category III Subjects (Post Unblinding of EN3835-302/303)

None

11.2.4. Exclusion Criteria Category I and II Subjects Who Opt to Receive Retreatment (Post Unblinding of EN3835-302/303)

A Category I or Category II subject will be excluded from retreatment if she:

1. Has any of the following systemic conditions:
    a. Coagulation disorder.
    b. Evidence or history of malignancy (other than excised basal-cell or squamous-cell carcinoma) unless there has been no recurrence in at least 5 years.
    c. History of keloidal scarring or abnormal wound healing.
    d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases should be discussed with the Medical Monitor.

e. Evidence of clinically significant abnormalities on physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory values.

2. Has any of the following local conditions in the areas to be treated:
   a. History of lower extremity thrombosis or post-thrombosis syndrome
   b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated
   c. Inflammation or active infection
   d. Severe skin laxity, flaccidity, and/or sagging
   e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
   f. Has a tattoo and/or a mole located within 2 cm of the site of injection
3. Requires the following concomitant medications before or during participation in retreatment portion the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before or 7 days after injection of study drug.
4. Is nursing or providing breast milk during the course of retreatment (Treatment Visit 1 through Treatment Visit 4).
5. Is pregnant or intends to become pregnant during the course of retreatment (Treatment Visit 1 through Treatment Visit 4).
6. Intends to use tanning spray or tanning booths in the 30 days prior to and during the course of retreatment (Treatment Visit 1 through Treatment Visit 4).
7. Has a known systemic allergy to collagenase or any other excipient of study drug.
8. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for retreatment.

11.3. Subject Discontinuation Criteria

A premature discontinuation will occur when a subject who signed informed consent ceases participation in the study, regardless of circumstances, prior to the completion of the protocol. Subjects can be prematurely discontinued from the study for one or more of the following reasons:

- An adverse event
- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, failure to meet inclusion/exclusion criteria after study entry)
- Treatment with placebo in EN3835-302/303 (determined after unblinding)
- Withdrawal by subject (reason must be specified)
- The subject was "lost to follow-up"
- Other reasons (reason must be specified, for example: the subject moved, pregnancy, Investigator decision, Sponsor decision to terminate trial, etc)

If a subject discontinues from the study, all end-of-study procedures including safety and efficacy assessments should be conducted as detailed in the relevant Schedule of Events (Section 5.1 through Section 5.4). The date a subject discontinues and the reason for discontinuation will be recorded in the source documentation and electronic case report form (eCRF). If, however, a subject withdraws consent, no end-of-study procedures and assessments are required (but are encouraged to reduce missing information) except the collection of adverse event (AE) information. This information should be recorded in the source documentation and the eCRF.

11.3.1. Replacement Procedures

Subjects who discontinue from the study will not be replaced.

12. TREATMENT OF SUBJECTS

12.1. Study Visits

The Schedule of Events for all subjects up through 180 days following studies EN3835-302/303 is provided in Section 5.1. Beyond Day 180, the Schedule of Events for subjects classified as categories I and II and who are eligible and opt to receive retreatment is provided in Section 5.2 and in observational phase of study Section 5.3. The Schedule of Events for subjects in Category II who are not eligible for retreatment, or are in Category I and II and who are eligible but opt not to have retreatment, is provided in Section 5.3. The Schedule of Events for Category III subjects is shown in Section 5.4. Below are further details where additional instruction about the assessments that will be performed is deemed to be needed.

Unscheduled visits may be done as deemed necessary at any time during the study to ensure subject safety; assessments done at unscheduled visits are at the discretion of the investigator.

12.1.1. Informed Consent

Signed and dated informed consent will be obtained from each subject before any study procedures are undertaken, or before any changes to the subject's medication regimen are made. Details about how the informed consent will be obtained and documented are provided in Section 21.3, Subject Information and Consent.

12.1.2. Subject Screening Screening A/ Day 71 Visit of Double-blind Study (± 14 Days)

Upon completion of Day 71 assessments in the double-blind study EN3835-302 or EN3835-303, a subject will be eligible to enter this open-label extension study. The status of all subjects (eg, screen fails) will be kept in the EDC system.

If the Screening Visit for a subject is greater than 14 days after the subject's Day 71 of study EN3835-302/303, only the unique Screening Visit assessments will be performed (informed consent, inclusion and exclusion criteria evaluation, height, weight, and physical examination). No subject will be allowed to enroll in the study if the Screening Visit does not occur within 180 days after Day 71 of Study EN3835-302/303. All changes in medical history occurring between completion of study EN3835-302/303 and the Screening Visit of study EN3835-304 will be considered adverse events and will be recorded and evaluated for seriousness and severity (see as appropriate, Section 14.1.1, Adverse Events or Section 14.1.2, Serious Adverse Events).

12.1.3. Medical History

Since this is a long-term rollover study for subjects that participated and completed the double-blind study (EN3835-302 or EN3835-303), in which the subjects' medical history was collected, only newly discovered medical history (events/procedures that occurred prior to enrollment in study EN3835-302/303) will be collected (eg, a subject remembers having an appendectomy as a child that was not reported in the medical history for EN3835-302/303).

12.1.4. Study Entry/Observational Assessments (Up to Day 180)

A subject who gives written informed consent and who satisfies all eligibility criteria (Section 11) may be entered into this open-label observational study and complete safety and cellulite severity assessments 180 days following their Day 71 Visit in the double-blind study, as detailed in Section 5.1. The subject identification number will be carried over from the double-blind, placebo-controlled study (EN3835-302/303).

12.1.5. Day 180/Early Termination Visit/Screening B

Subjects who received active treatment will return at 180 days (±14 days) following their Screening Visit (Day 71 of the double-blind studies [EN3835-302 or EN3835-303]) for cellulite severity assessments. All assessments will be completed as detailed in Section 5.1 prior to unblinding of the subject's treatment assignment in the double-blind study. Local safety assessments (Section 14.6.1) and adverse events will be monitored (Section 14). A subject who terminates study participation between Day 71 and Day 180 will have an Early Termination Visit that includes the assessments listed for Visit 1 Day 180.

If unblinding of drug treatment in EN3835-302/303 occurs by the Sponsor prior to a subject's Day 180 visit, Investigators, subjects and site personnel will remain blinded to the subject's drug treatment in the double-blind studies until after the Day 180 assessment have been completed. After assessments are completed, unblinding will occur at the site and subjects who received placebo will be discontinued, and subjects who received active EN3835 will be classified into one of three categories based on responder status of each of their buttocks in the double-blind study (Section 10.1). If the subject is categorized to a classification and has ratings that qualify for retreatment (ie, all Category I subjects will be offered retreatment; Category II subjects that have at least a 1-level composite response reduction compared to Day 71 of the EN3835-302/303 study AND no longer maintain a 2-level composite response compared to baseline in the EN3835-302/303 study on either or both buttocks) the subject may be offered retreatment. If there is a composite worsening of cellulite severity of 1-level (ie, worsening of both the PR-PCSS and CR-PCSS by at least 1 severity levels) detected in a Category II subject, the confirmation of loss of response will be established during a follow-up visit ~2 weeks after the loss of response is detected at Day 180 as described in Section 12.2.2.3 (Confirmation Visit). If a Category I subject accepts the offer of retreatment at the Day 180 visit, Screening B of the Treatment Phase of the protocol may occur on the same day as the Day 180 Visit. If the loss of response in a Category II subject is confirmed and the subject accepts the offer of retreatment at the Confirmation Visit, Screening B of the Treatment Phase may occur on the same day as the Confirmation Visit. If the loss of response is not confirmed, the subject will be considered to not have lost response and will not be offered retreatment.

If the unblinding has not occurred by a subject's Day 180 visit, an Unscheduled Visit will be arranged after unblinding has occurred (see Section 12.4) and the subjects will be classified at this Unscheduled Visit or, if received placebo, will be discontinued. If a Category I subject decides to accept the offer of retreatment, the subject may be screened (Screening B Visit of the Treatment Phase) during the Unscheduled Visit. If a Category II meets eligibility criteria for retreatment during the Unscheduled Visit, the loss of response will be confirmed during a follow-up visit ~2 weeks after the loss of response is detected as described in Section 12.2.2.3 (Confirmation Visit). If the loss of response in a Category II subject is confirmed and the subject

accepts the offer of retreatment at the Confirmation Visit, Screening B of the Treatment Phase may occur on the same day as the Confirmation Visit. If the loss of response is not confirmed, the subject will be considered to not have lost response and will not be offered retreatment.

If a subject does not meet Screening B criteria (eg, positive pregnancy test, elevated liver enzymes, etc), the subject maybe rescreened at a later date.

As stated in Section 10.1, either on Day 180 Visit after assessments have been completed or at an Unscheduled Visit, once the study blind is broken, the EN3835-302/303 placebo subjects will be discontinued, and subjects who received active EN3835 in their respective double-blind study will be classified into one of three categories based on their response in the double-blind study.

12.2. Category I Subjects and Category II Subjects Visits (Post Unblinding of EN3835-302/303)

Assessments to be completed at these visits are detailed in Section 5.2 (Treatment Assessments) and in Section 5.3 (Observation Assessments).

Beginning at Day 180 (ie, approximately 6 months after Day 71 Visit of the double-blind study), after Day 180 assessments have been completed in a blinded fashion, all eligible Category I subjects will be offered a course of retreatment. Category II subjects who have had at least a 1-level composite response reduction compared to Day 71 of the EN3835-302/303 study AND no longer maintain a 2-level composite response compared to baseline in the EN3835-302/303 study will be offered a course of retreatment; and assessments to be completed at these Treatment Assessments are detailed in Section 5.2. After completing Day 71 of the retreatment in this open-label study, the subjects will be assessed at intervals for cellulite severity and safety as detailed in Section 5.3 until they have completed approximately 3 years (1080 days) from Day 71 of the double-blind study. Category II subjects that have not shown a 1-level composite reduction (ie, have maintained a successful response), and/or Category I and/or Category II subjects who are eligible for a retreatment course but opt not to receive retreatment will be assessed at intervals (Section 5.3) for cellulite severity and safety until they have completed approximately 3 years from Day 71 of the double-blind study. If the subject's buttocks become eligible for retreatment based on the ratings of an observational visit and if they have not already received a course of retreatment, they will be offered retreatment up to including Observational Visit 5 (Month 36). The TRR for composite 1-level responders (ie, Category I) will also be assessed at 180 days after the Day 71 Visit of the double-blind study as well as after Treatment Visit 4 (Retreatment Day 71) of this open-label study for those buttocks that are retreated. Buttocks not retreated will be assessed at each of the observation visits as shown in Section 5.3. TRR is defined as a 1-level composite worsening of cellulite severity levels (on both the PR-PCSS and CR-PCSS).

If a treatment period eclipses (or overlaps) a scheduled observational visit, the observational visit will be skipped and the subject will re-enter the observational schedule at the next interval visit. For example, if a subject initiated retreatment on Day 351 (which would then be Treatment Visit 1), the treatment period would proceed for approximately 71 days until Day 421 (Treatment Visit 4) and the Observational Visit at Day 360 would be skipped; the subject's next observational visit would be Day 540.

Treatments will not be offered to any subject after Visit 5 (Day 1080 ± 30 days; Month 36 ± 1 month).

12.2.1. Treatment Assessments (Treatment is Optional for Eligible Subjects)

12.2.1.1. Screening B (Days -14 to -1 Relative to Treatment Visit 1)

The following procedures will be performed and documented during Screening B:

1. Obtain written informed consent (Section 12.1.1)
2. Evaluate eligibility based on inclusion/exclusion criteria (Section 11.1 and Section 11.2)
3. Subject will have digital photographs taken of her two buttocks (Section 13.1.1)
4. Subjects will get instruction on the use of the PR-PCSS (Section 13.1.2.1) and review training and use materials
5. Prior to Investigator CR-PCSS assessment, subjects will rate each of their two buttocks using the PR-PCSS while viewing their digital images (Section 13.1.2.1); the Investigator is blinded to these scores
6. Subjects will review subject cellulite assessment training and use materials prior to use of the S-GAIS, PR-CIS, Subject Satisfaction with Cellulite Treatment Assessment, and the SSRS
7. Subject Global Aesthetic Improvement Scale (S-GAIS) (Section 13.1.2.2); subjects will rate each of their two buttocks while viewing pretreatment images from Day 1 of the double-blind study (EN3835-302/303)
8. Patient Reported Cellulite Impact Scale (PR-CIS) assessment (Section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock
9. Subject will complete the Subject Satisfaction with Cellulite Treatment Assessment (Section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock
10. Subject will complete the Subject Self-Rating Scale (SSRS) (Section 13.1.2.5); note this assessment is of both left and right buttocks rather than each individual buttock
11. After the subject has completed the PR-PCSS ratings and after the Investigator has reviewed the training and use material for the CR-PCSS, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (Section 13.1.2.6); the subject is blinded to these ratings. The ratings from the PR-PCSS and CR-PCSS will be used to assess eligibility of the buttocks for retreatment
12. Record prior and concomitant medications/procedures (Section 12.5)
13. Physical examination including measurement of body weight and height (Section 14.11)
14. Vital sign measurements (Section 14.9)
15. 12-lead ECG (Section 14.10)

16. Collection of samples for:
    a. Clinical laboratory testing (Section 14.7)
    b. Anti-AUX-I and anti-AUX-II antibody testing (Section 14.8)
    c. Serum pregnancy testing (Section 14.7)
17. Injection site reactions/local tolerability in the buttocks (Section 14.6.1)
18. Adverse events (Section 14)

12.2.1.2. Selecting and Marking Dimples During Treatment Visits

Selection of dimples to be treated in the eligible buttocks is at the discretion of the Investigator. Dimples must be well-defined and evident when the subject is standing in a consistent, standardized relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). Category I subjects and Category II subjects eligible for retreatment can receive up to 3 retreatment visits of study drug as outlined in Section 5.2 unless the buttock is dimple-free (score of 0 on CR-PCSS as reported by the Investigator) at Treatment Visit 1, Treatment Visit 2 and/or Treatment Visit 3. During each retreatment visit, the buttocks to be treated will be photographed before and after marking dimples and injection sites while the subject is standing in a consistent, standardized relaxed pose as described in the Photography Manual. The cellulite severity assessments using the PR-PCSS and the CR-PCSS will be completed prior to marking dimples and injection sites.

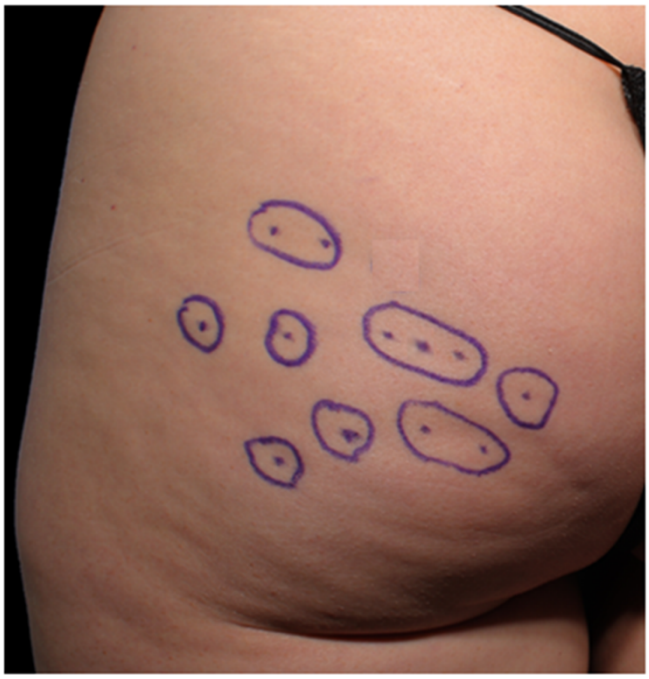
The Investigator or qualified designee will select dimples within each buttock that are well-defined, evident when the subject is standing, and suitable for retreatment; retreatment consists of 12 injections per buttock (up to 24 injections total in two buttocks) per retreatment visit. Because the goal of retreatment is to improve the aesthetic appearance of each entire buttock, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of each entire buttock. The same dimples within a buttock or different dimples within a buttock may be retreated at the designated treatment visits but injections must all be within the buttocks (12 injections per buttock) for all 3 visits. Each eligible buttock will receive all 3 treatment visits unless the buttock has no treatable EFP dimples and the Investigator rates the buttock a score of 0 on the CR-PCSS. If no injections in a particular buttock (right or left) are given at Treatment Visit 2, subjects will still be assessed for retreatment in the contralateral buttock (if eligible) at Treatment Visit 2 if the buttock was retreated at Treatment Visit 1, and when they return for Treatment Visit 3, each of the buttocks will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS). If the Investigator rates either or both of the buttocks greater than 0 on the CR-PCSS, injections at Treatment Visit 3 should be given.

For each dimple selected for retreatment, the Investigator or qualified designee will choose injection sites (injection sites within a dimple should be spaced approximately 2 cm apart, if a dimple requires more than 1 injection; locating at least one injection site at the nadir, if present, of the dimple). Each injection site will be marked with a “dot” using a surgical marker. For round dimples, the “dot” will be placed in the center of the dimple; for elongated dimples, “dots” will be spaced out approximately 2 cm along the longer axis of the dimple. The Investigator or qualified designee will then use a surgical marker to circle each of the dimples selected for treatment. Circles in the buttock should not overlap.

Each of the buttocks to be retreated will be photographed before and after marking dimples and injection sites while the subject is standing in a consistent, standardized relaxed pose as described in the Photography Manual.

Examples of subject dimple and injection site markings are shown as follows:

Sample Buttock Marking



12.2.1.3. Digital Photography during Treatment Visits 1, 2, and 3

During each retreatment visit, each of the buttocks will be photographed before and after marking dimples and injections sites while the subject is standing in a consistent, standardized relaxed pose as described in Section 13.1.1.

12.2.1.4. Treatment Visit 1

12.2.1.4.1. Treatment Visit 1: Pre-Injection

For each subject, the Sponsor will inform the site of the areas eligible for retreatment based on the PR-PCSS/CR-PCSS ratings obtained during Treatment Visit 1. Each buttock will be photographed during the retreatment visits. Prior to injection, the following procedures will be conducted:

1. Take digital photography of each buttock before marking dimples and injection sites on the buttocks being retreated (Section 13.1.1). Note: both buttocks will be photographed, regardless of treatment.
2. Subjects will get instruction on the use of the PR-PCSS (Patient Instructions for Use of PR-PCSS) and review training and use materials.

3. Subjects will rate each of their buttocks using the PR-PCSS (Section 13.1.2.1); the Investigator is blinded to these scores.
4. The Investigator will review training and materials for the use of the CR-PCSS.
5. The Investigator will conduct live assessments of subject's cellulite severity of each of the buttocks using the CR-PCSS (Section 13.1.2.6); the subject is blinded to these ratings.
6. Record concomitant medications/procedures (Section 12.5).
7. Vital sign measurements (Section 14.9).
8. Collection of samples for:
    a. Urine pregnancy testing (Section 14.7).
9. Select and mark dimples to be treated in each of the buttocks (Section 12.2.1.2).
10. Take digital photograph of each of the buttocks after marking dimples and injection sites (Section 13.1.1).
11. For eligible buttock(s), obtain kit number(s) of study treatment.

12.2.1.4.2. Treatment Visit 1: Injection and Post-injection

1. Administration of study drug in the prone position (Section 10.3).
2. Record number of dimples treated and number of injections administered in each of the buttocks being retreated.
3. Vital sign measurements (Section 14.9).
4. Injection site reactions and local tolerability (Section 14.6.1).
5. Adverse events (Section 14).

12.2.1.5. Treatment Visits 2 and 3 (Day 22 ± 3 days and Day 43 ± 3 days)

12.2.1.5.1. Treatment Visits 2 and 3: Pre-injection

1. Record concomitant medications/procedures (Section 12.5).
2. Body weight measurements.
3. Vital sign measurements (Section 14.9).
4. Collection of samples for:
    a. Anti-AUX-I and anti-AUX-II antibody testing (Section 14.8)
    b. Urine pregnancy testing (Section 14.7)
5. Digital photographs of the buttock(s) receiving retreatment before marking dimples and injection sites (Section 13.1.1). Note: both buttocks will be photographed, regardless of treatment.

6. Subject Cellulite Assessments, after review of training and use materials, of each of the buttocks using the photographic image of each buttock before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) in the following sequential order using:
    a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (Section 13.1.2.1).
7. Investigator Cellulite Assessments conducted, after review of training and use material, of each of the buttocks receiving retreatment prior to marking dimples and injection sites using:
    a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (Section 13.1.2.6).
8. Select and mark dimples to be treated in each buttock receiving retreatment (Section 12.2.1.2).
9. Digital photographs of each buttock after marking dimples and injection sites (Section 13.1.1).
10. For eligible buttock(s), obtain kit number(s) of study treatment.

12.2.1.5.2. Treatment Visits 2 and 3: Injection and Post-injection

1. Administration of study drug in the prone position (Section 10.3).
2. Record number of dimples treated and number of injections administered in each buttock being retreated.
3. Vital sign measurements (Section 14.9).
4. Injection site reactions and local tolerability (Section 14.6.1).
5. Adverse events (Section 14).

12.2.1.6. Treatment Visit 4 (Day 71 + 5 days)

The following procedures will be performed at Visit 4:

1. Record concomitant medications/procedures (Section 12.5).
2. Measurement of body weight.
3. Vital sign measurements (Section 14.9).
4. Collection of samples for:
    a. Clinical laboratory testing (Section 14.7).
    b. Urine pregnancy test (Section 14.7).
    c. Anti-AUX-I and anti-AUX-II antibody testing (Section 14.8).
5. Digital photographs of the buttock(s) receiving retreatment (Section 13.1.1).
6. Subject will review training and use materials for the PR-PCSS, S-GAIS, PR-CIS, Subject Satisfaction with Cellulite Treatment Assessment, and SSRS.

7. Subject Cellulite Assessment of each retreated buttock using the photographic image (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using:
    a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (Section 13.1.2.1).
    b. Subject Global Aesthetic Improvement Scale (S-GAIS) (Section 13.1.2.2); subjects will rate each of their two buttocks while viewing pretreatment images from Day 1 of the double-blind study (EN3835-302/303).
    c. Patient Reported Cellulite Impact Scale (PR-CIS) assessment (Section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock while viewing images from Treatment Visit 4 (Day 71) of EN3835-304.
    d. Subject will complete the Subject Satisfaction with Cellulite Treatment Assessment (Section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock and is conducted while viewing images from Treatment Visit 4.
    e. Subject will complete the Subject Self-Rating Scale (SSRS) (Section 13.1.2.5); note this assessment is of both left and right buttocks rather than each individual buttock.
8. Investigator Cellulite Assessments will be conducted, after the review of training and use material for the CR-PCSS, of each of the buttock(s) receiving retreatment using:
    a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (Section 13.1.2.6).
9. Injection site reactions and local tolerability (Section 14.6.1).
10. Adverse events (Section 14).

After Treatment Visit 4, retreated subjects enter/re-enter the observational phase of the study with assessments of safety and TRR. If an observational visit was scheduled to occur during a Treatment Phase visit (Screening B through Treatment Visit 4), the observational visit would be skipped and the subject would enter/re-enter the Observation Phase visits at the next interval visit.

12.2.2. Observation Assessments

12.2.2.1. Observation Visit 2 (Day 360 Relative to Day 71 of the Double-blind Study)

1. Obtain written informed consent (Section 12.1.1).
2. Evaluate eligibility based on inclusion/exclusion criteria (Section 11.1 and Section 11.2).
3. Subject will have digital photographs taken of each of the buttocks (Section 13.1.1).
4. Subjects will get instruction on the use of the PR-PCSS (Section 13.1.2.1) and review training and use materials for the PR-PCSS, the PR-CIS, the SSRS and the Subject Satisfaction with Cellulite Treatment assessments.
5. Prior to Investigator CR-PCSS assessment, subjects will rate each of their two buttocks using the PR-PCSS while viewing their digital images (Section 13.1.2.1); the Investigator is blinded to these scores.

6. Subject Global Aesthetic Improvement Scale (S-GAIS) (Section 13.1.2.2); subjects will rate each of their two buttocks while viewing pretreatment image from Day 1 of the double-blind study (EN3835-302/303).
7. Patient Reported Cellulite Impact Scale (PR-CIS) assessment (Section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock.
8. Subject will complete the Subject Satisfaction with Cellulite Treatment Assessment (Section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock.
9. Subject will complete the Subject Self-Rating Scale (SSRS) (Section 13.1.2.5); note this assessment is of both left and right buttocks rather than each individual buttock.
10. After the subject has completed the PR-PCSS ratings and after the Investigator reviews the training and use materials for the CR-PCSS, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (Section 13.1.2.6); the subject is to remain blinded to these ratings.
11. Record prior and concomitant medications/procedures (Section 12.5).
12. Collection of samples for:
    a. Anti-AUX-I and anti-AUX-II antibody testing (Section 14.8).
13. Local safety assessments (Section 14.6.1).
14. Adverse events (Section 14).

12.2.2.2. Observation Visits 3-5/EOS/Early Termination (Day 540 – Day 1080/EOS/Early Termination)

1. Record concomitant medications/procedures (Section 12.5).
2. Collection of samples for:
    a. Anti-AUX-I and anti-AUX-II antibody testing (Section 14.8).
3. Digital photographs of each of the buttocks (Section 13.1.1).
4. Subjects will get instruction on the use of the PR-PCSS (Section 13.1.2.1) and review training and use materials for the PR-PCSS, S-GAIS, PR-CIS, SSRS, and the Subject Satisfaction with Cellulite Treatment assessments.
5. Subject Cellulite Assessment of each of the two buttocks using the photographic image (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using:
    a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (Section 13.1.2.1).
    b. Subject Global Aesthetic Improvement Scale (S-GAIS) (Section 13.1.2.2); subjects will rate each of their two buttocks while viewing pretreatment image from Day 1 of the double-blind study (EN3835-302/303).
6. Patient Reported Cellulite Impact Scale (PR-CIS) assessment (Section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock.

7. Subject will complete the Subject Satisfaction with Cellulite Treatment Assessment (Section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock.
8. Subject will complete the Subject Self-Rating Scale (SSRS) (Section 13.1.2.5); note this assessment is of both left and right buttocks rather than each individual buttock.
9. Investigator Cellulite Assessments will be conducted, after the Investigator reviews training and use materials for the CR-PCSS, of each of the buttocks live using:
10. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (Section 13.1.2.6).
11. Check ePRO for a potential requirement for a confirmation visit.
12. Local safety assessments (Section 14.6.1).
13. Adverse events (Section 14).

12.2.2.3. Confirmation Visits

Time to reduction of a ≥1 level and/or ≥2-level composite improvement in cellulite severity compared to the level at Day 71 of the double-blind study will be assessed by both the PR-PCSS and the CR-PCSS. If, during the study, there is a composite worsening of cellulite severity of 1-level (ie, worsening of both the PR-PCSS and CR-PCSS by 1 severity levels), the confirmation of loss of response will be established during a follow-up visit ~2 weeks after the loss of response is first detected. The following procedures will be completed at the Confirmation Visits:

1. Digital photographs of each of the buttocks.
2. Subject Cellulite Assessment of each of the two buttocks, after reviewing the training and use materials, using the photographic image (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using:
    a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (Section 13.1.2.1).
3. Investigator Cellulite Assessments of each of the buttocks, after reviewing the training and use material, using:
    a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (Section 13.1.2.6).

NOTE: Subjects showing a *confirmed* composite worsening of cellulite severity of 1-level will be offered retreatment and will continue with annual safety and immunogenicity assessments for up to 3 years after Day 71. Subjects who do NOT show a confirmed composite worsening of cellulite will be considered to not have a worsening, will not be offered retreatment, and will continue with annual safety and immunogenicity assessment for up to 3 years after Day 71.

12.3. Category III Subjects Visits (Post Unblinding of EN3835-302/303)

Assessments to be completed at these visits are detailed in Section 5.4. Category III subjects are to return every 6 months during the first two years and then annually until they have completed 1080 days (3 years) following Day 71 of the double-blind study for safety evaluations. Category III subjects receive no additional treatments during the study.

12.3.1. Observation Visits 2-5/EOS/Early Termination (Day 360 – Day 1080/EOS/Early Termination)

1. Obtain written informed consent (Section 12.1.1).
2. Evaluate eligibility based on inclusion/exclusion criteria (Section 11.1 and Section 11.2).
3. Record concomitant medications/procedures (Section 12.5).
4. Collection of samples for:
    a. Anti-AUX-I and anti-AUX-II antibody testing (Section 14.8).
5. Local safety assessments (Section 14.6.1).
6. Adverse events (Section 14).

12.4. Unscheduled Visit

If any subject needs to return to the site prior to her next scheduled visit, site staff should follow the Unscheduled Visit procedures outlined in Section 5. Site staff may conduct additional study procedures if required, however no photographs or cellulite severity assessments will be done at unscheduled visits.

If unblinding of Investigator, subject and site personnel to the treatment that the subject received in the double-blind study EN3835-302/303 does not occur on Day 180 Visit after all assessments are completed, then an unscheduled visit may be arranged to unblind the subject to the treatment received. Following unblinding of EN3835-302/303, subjects who received placebo will be discontinued, and subjects who received active EN3835 will be classified into one of three categories based on responder status (Section 10.1) and proceed as described in Section 12.1.

12.5. Prior and Concomitant Medications and Procedures

All prior medications will be recorded; the word ‘prior’ refers to the period from the last visit from the previous Phase 3 clinical study through the signing of informed consent in the EN3835-304 study.

All concomitant medications (including over-the-counter medications) including those to treat EFP, taken by the subject during the course of the EN3835-304 study (ie, after informed consent for EN3835-304 is signed) will be recorded.

Additionally, any diagnostic, therapeutic or surgical procedures performed during the study period should be recorded including the date, indication for and description of the procedure.

12.5.1. Prohibited Medications or Procedures

For eligible Category I and Category II subjects who opt for retreatment, the following medications are prohibited during the retreatment phase of the study (Table 4): anticoagulants (warfarin, heparin, direct thrombin inhibitors, Factor X inhibitors) and antiplatelet agents (aspirin >150 mg/day and P2Y12 inhibitors, such as clopidogrel), which can cause additional bruising. However the use of aspirin at a dose level of ≤150 mg per day will be permitted during this time.

Table 4: Concomitant Medication Restrictions for Category I and Category II Subjects During the Retreatment Phase of Study (Treatment Visits 1 - 4)

Drug Class	Restrictions
Anticoagulants	Subjects cannot take antiplatelet agents or anticoagulants (except for ≤150 mg aspirin daily) within 7 days before and 7 days after the dosing administration.

12.6. Treatment Compliance

Eligible Category I and/or Category II subjects may receive study drug administered by an Investigator at the Investigator's site.

Accidental or intentional overdoses should be reported to the Sponsor/designee promptly (see Section 14.6.2.1, Overdose).

For Category III subjects and Category I and Category II subjects that opt not to receive treatment, this study is observational in nature, and no additional treatments are to be administered.

13. ASSESSMENT OF EFFICACY

13.1. Efficacy Measurements

13.1.1. Digital Photography

Although digital photographs are not direct efficacy measurements, digital photography will be utilized in the assessment of certain efficacy measurements to assess certain cellulite severity parameters at specific intervals (see Section 5.1 through Section 5.3, Schedule of Events). After Day 180 Visit and unblinding of the double-blind studies EN3835-302/303, photography will be limited to Category I and Category II subjects. At each designated visit requiring photography, the Investigator or qualified designee will photograph each region using a Sponsor-supplied standardized digital camera in a standardized manner. The subject will be standing for each photography session and will be wearing a standardized photographic garment as described in the Photography Manual. The Investigator or qualified designee will photograph each targeted region while the subject is standing in a consistent, standardized relaxed standing pose, ie, standing position with relaxed gluteus muscles.

All photographs from this study are the property of Endo and may be utilized for clinical development, scientific communication, marketing, regulatory purposes, and/or legal applications as required/desired by Endo.

13.1.2. Subject and Investigator Cellulite Assessments

Investigator cellulite assessments are independent of the subject assessments. Therefore, all subject cellulite assessments must be completed before the Investigator's cellulite assessments are initiated. The subject assessments will be done using a subject-assigned password protected electronic patient reported outcome (ePRO) system and the Investigator and study site personnel will not have access to the subject's assessments or password; the clinician assessments will be recorded in an investigator-assigned password protected system and the subject will not have access to the Investigator's assessments or password. Subject assessments will be done alone with no study site personnel in the room. Investigators will be instructed not to verbalize their ratings while in the presence of the subject.

13.1.2.1. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)

The PR-PCSS will be conducted for the purpose of assessing the severity of cellulite in the buttock. The scale is a 5-level photonumeric scale developed specifically for patients and used by the subject to assess the severity of their cellulite by viewing digital images of each of their buttocks captured by photography at the visit; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the subject in the assessments.

At Screening (eg, Day 71/EOS of the double-blind study) and at the beginning of each visit where photography is to be captured, subjects will have digital photographs taken of each of their buttock(s). Subjects will be given instructions in the proper use (Patient Instructions for Use of PR-PCSS) of the PR-PCSS, will review training and use material, and then perform the PR-PCSS for each of the targeted areas (Appendix B). While viewing the digital images of each of their buttocks on a standardized computer monitor and using the PR-PCSS for buttock, subjects will be instructed to answer the following question for each buttock: *Today, how would*

you rate the severity of your cellulite in the area displayed using the PR-PCSS? The subject will be given the following explanations*: Please try to match the severity of your cellulite, as seen in this digital image, with one of the cellulite levels on the PR-PCSS. Please look at the image of your cellulite and the pictures, labels, and descriptions on the PR-PCSS carefully before selecting your answer. If you feel that your cellulite level is between 2 of the levels, please select the level that is closest to your image. If you feel that your cellulite is exactly halfway between two PR-PCSS levels of cellulite severity, please select the more severe response.*

The subject will enter their rating electronically into an ePRO system; the Investigator and other site personnel will be blinded to the rating entered by the subject. This variable will be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.

13.1.2.2. Subject Global Aesthetic Improvement Scale (S-GAIS)

At each of the visits designated to capture the S-GAIS in Section 5.1 through Section 5.3, subjects will review training and use materials for S-GAIS, and complete the S-GAIS for each of the buttocks as described below using the pretreatment Day 1 digital image (Baseline) from the double-blind studies (EN3835-302/303) of each of the buttocks for comparison.

All treated subjects will be instructed to answer the following question for each buttock:

How would you rate the appearance of your treated cellulite after treatment?

The S-GAIS assessment will occur after the subject has completed the PR-PCSS assessment to avoid introducing potential bias to the static PR-PCSS assessment. The subject will view each of their pretreatment Day 1 digital images from the double-blind study (EN3835-302/303) alongside their current study visit digital images of each of their buttocks to aid in the assessment (Table 5). Subjects will provide a rating from those below that best represents their answer for each treated buttock.

This variable will be entered directly into the ePRO system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.

Table 5: Subject Global Aesthetic Improvement Scale (S-GAIS)

Rating	Response Option	Description
+3	Very much improved	My treated cellulite looks very much better.
+2	Much improved	My treated cellulite looks much better, but additional treatment would slightly improve the result.
+1	Improved	My treated cellulite looks better, but additional treatment is necessary.
0	No change	My treated cellulite looks essentially the same as it did originally.
−1	Worse	My treated cellulite looks worse than it did originally.
−2	Much worse	My treated cellulite looks much worse than it did originally.
−3	Very much worse	My treated cellulite looks very much worse than it did originally.

13.1.2.3. Patient Reported Cellulite Impact Scale (PR-CIS)

At each of the visits designated to capture the PR-CIS in Section 5.1 through Section 5.3; subjects will review training and use materials, and will be instructed to answer 6 questions related to the areas selected for treatment on their buttocks on the Patient Reported Cellulite Impact Scale (Appendix D) while viewing digital images of their buttocks. The PR-CIS assesses the visual and emotional impact of cellulite (happy, bothered, self-conscious, embarrassed, looking older or looking overweight or out of shape) using a 6-question survey, with each question rated from 0 (not at all) to 10 (extremely).

A PR-CIS total score and an abbreviated PR-CIS score (excluding question 5) will be derived from these 6 individual questions.

This variable will be entered directly into the ePRO system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable

13.1.2.4. Subject Satisfaction with Cellulite Treatment Assessment

At the designated visits, subjects will review training materials and will be instructed to answer a question related to their treated buttocks while viewing digital images of their buttocks. The subject will view each of their pretreatment Day 1 digital images from the double-blind study (EN3835-302/303) alongside their current study visit digital images of their buttocks to aid in the assessment.

Subjects will be given a list of responses and they will provide a rating from those below that best represents their answer (Table 6).

Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks that were treated?

This variable will be entered directly into the ePRO system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.

Table 6: Subject Satisfaction with Cellulite Treatment Assessment - Buttocks

Rating	Description
+2	I am very satisfied with the cellulite treatment on my buttocks.
+1	I am satisfied with the cellulite treatment on my buttocks.
0	I am neither dissatisfied nor satisfied with the cellulite treatment on my buttocks.
-1	I am dissatisfied with the cellulite treatment on my buttocks.
-2	I am very dissatisfied with the cellulite treatment on my buttocks.

13.1.2.5. Subject Self-Rating Scale (SSRS)

The SSRS is a measure that assesses subject satisfaction with appearance in association with cellulite on the buttocks using whole numbers on a 7-level scale that ranges from 0 (extremely dissatisfied to 6 (extremely satisfied). The subject will review training and use materials for the SSRS. The subject will be asked to respond to the question related to the satisfaction with appearance of the cellulite on their buttocks. No photographs or reference to previous ratings or

evaluations will be used. Subjects will be given a list of responses and they will provide a rating from those below that best represents their answer (Table 7).

To complete the SSRS, subjects will be instructed to answer: *Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time whether or not in your judgment it is due entirely to treatment with EN3835?*

This variable will be entered directly into the ePRO system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.

Table 7: Subject Self-Rating Scale (SSRS)

Rating	Response Option
6	Extremely satisfied
5	Satisfied
4	Slightly satisfied
3	Neither satisfied nor dissatisfied
2	Slightly dissatisfied
1	Dissatisfied
0	Extremely dissatisfied

13.1.2.6. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)

The CR-PCSS will be conducted for the purpose of assessing the severity of cellulite in the buttock. The scale is a 5-level photonumeric scale developed specifically for clinicians and used by the Investigator to assess the severity of the subject's cellulite in each buttock by live assessments; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the Investigator in the assessments.

Investigators will be trained and qualified on the use of the CR-PCSS prior to assessing any subjects. Investigators will review training and use materials at each visit prior to the use of the CR-PCSS.

At the Day 71 visit during the double-blind study (which also serves as the Screening visit for the current study), the Investigator will determine severity of cellulite of each of the two buttocks via live assessment of the subject using the CR-PCSS for the buttock (Appendix C) after the subject has completed her self-assessment using the PR-PCSS for the buttock (Appendix B). Investigators will evaluate each of the two buttocks by live assessments using the CR-PCSS for the buttock to make his/her evaluation. At each visit, the Investigator will make his/her assessment independently and after the subject has conducted her self-assessment using the PR-PCSS.

This variable will be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.

14. ASSESSMENT OF SAFETY

14.1. Definitions

14.1.1. Adverse Events

An adverse event (AE) is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (eg, chemistry, ECG, X-ray, etc), or worsening of a pre-existing condition associated temporally with the use of the study medication whether or not considered related to the study medication. Adverse events will be captured once a subject has signed the informed consent. All AEs that are reported between the completion of studies EN3835-302/303 and the Day 180 Visit will be recorded and evaluated as appropriate.

AEs include:

- Changes in the general condition of the subject
- Subjective symptoms offered by or elicited from the subject
- Objective signs observed by the Investigator or other study personnel
- All concurrent diseases that occur after the start of the study, including any change in severity or frequency of pre-existing disease
- All clinically relevant laboratory abnormalities or physical findings that occur during the study

A treatment-emergent adverse event (TEAE) is any condition that was not present prior to treatment with study medication but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

All AEs, including both observed and/or volunteered problems, complaints, signs or symptoms must be recorded on the AE page of the eCRF, regardless of whether associated with the use of study medication. This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states (excluding the disease under study). A condition present at baseline that worsens after initiation of study treatment will be captured as an AE; the onset date will be the date the event worsened. The AE should be recorded in standard medical terminology when possible.

14.1.2. Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that:

- Results in death
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death)

- Results in or prolongs an inpatient hospitalization (NOTE: a hospitalization for elective or pre-planned surgery, procedure, or drug therapy does not constitute an SAE)
- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect (in offspring of a subject using the study medication regardless of time to diagnosis)
- Is considered an important medical event

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes. Examples of important medical events include malignancy, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.2. Monitoring Adverse Events

At each visit, subjects will be queried regarding any AEs that have occurred since the last visit. Subjects will be asked to volunteer information concerning AEs with a non-leading question such as, "How do you feel?" Study site personnel will then record all pertinent information in the source documents and the eCRF. The study drug compliance record should also be reviewed to detect potential overdoses (intentional/unintentional).

14.3. Relationship to Study Drug

The degree of "relatedness" of the AE to the study medication must be described using the following scale:

- **Not related** indicates that the AE is definitely not related to the study medication.
- **Unlikely related** indicates that there are other, more likely causes and study medication is not suspected as a cause.
- **Possibly related** indicates that a direct cause and effect relationship between study medication and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by the study medication.
- **Probably related** indicates that there is evidence suggesting a direct cause and effect relationship between the AE and the study medication.

It is the Sponsor's policy to consider "Probably related" and "Possibly related" causality assessments as positive causality. "Not related" and "Unlikely related" causality assessments are considered as negative causality.

Assessments will be recorded on the eCRF and must indicate clearly the relationship being assessed. For example, an AE that appears during a placebo run-in phase would be assessed with respect to the placebo treatment received and/or study procedures conducted during this phase. If

the AE continued into an active treatment phase, the relationship would be assessed for the active treatment phase only if the AE worsened.

14.4. Intensity Assessment

The intensity (or severity) of AEs is characterized as mild, moderate, or severe:

- **Mild** AEs are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- **Moderate** AEs introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- **Severe** AEs interrupt a subject's usual daily activity and typically require systemic drug therapy or other treatment.

When the intensity category of an AE changes, the greatest intensity during that continuous episode should be recorded.

14.5. Reporting Adverse Events and Serious Adverse Events

14.5.1. Reporting Adverse Events

Throughout the study, AEs will be documented on the source document and on the appropriate page of the eCRF whether or not considered treatment-related. This includes any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness. The Investigator is responsible for assessing the relationship of AEs to the study medication; relationship will be classified as not related, unlikely related, possibly related, or probably related.

All AEs will be collected by the Investigator from the time of signing the informed consent through 28 days after the last dose of study medication; this includes any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first.

14.5.2. Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study must be reported via email or fax by the Investigator using the Endo Clinical Trial Report Form for SAEs within 24 hours of first becoming aware of the SAE. SAEs will be collected by the Investigator from the time of signing the informed consent through 28 days after the last dose of study medication. SAEs that occur within 28 days, following cessation of the study treatment, or within 30 days, following premature discontinuation from the study for any reason, must also be reported within the same timeframe. Any SAE that is felt by the Investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the Sponsor within 24 hours of receipt by the Investigator.

All SAEs will be followed until resolution, stabilization of condition, or until follow-up is no longer possible.

In the event discussion is necessary regarding treatment of a subject, call the Medical Monitor (see contact information in Section 3).

All SAEs should be sent via the email address, or faxed to the fax number, provided in Section 3.

The Sponsor will determine whether the SAE must be reported within 7 or 15 days to regulatory authorities in compliance with local and regional law. If so, the Sponsor (or the Sponsor's representative) will report the event to the appropriate regulatory authorities. The Investigator will report SAEs to the IRB per their IRB policy.

14.5.2.1. Follow-up Procedures for Serious Adverse Events

To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, and the like should be obtained. In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and any autopsy report. These records should be reviewed in detail, and the Investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the follow-up SAE form and the Investigator should consider whether the event is related or not related to study drug.

14.6. Special Reporting Situations

14.6.1. Adverse Events of Special Interest

Adverse events such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis, will be recorded and evaluated for seriousness and severity (see Section 14.1.1, Adverse Events or Section 14.1.2, Serious Adverse Events).

In addition, local AEs associated with the injection site (whether the site was injected in the double-blind study (EN3835/302/303) or in this open-label study (EN3835-304)), including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, peau d'orange changes) cutaneous adverse events, will be recorded and evaluated for seriousness and severity (as appropriate, see Section 14.1.1, Adverse Events or Section 14.1.2, Serious Adverse Events).

14.6.2. Overdose/Misuse/Abuse

14.6.2.1. Overdose

Study drug overdose is any accidental or intentional use of study drug in an amount higher than the dose indicated by the protocol for that subject. Study drug compliance (see Section 12.6) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study drug overdose during the study should be noted on the study medication eCRF.

An overdose is not an AE per se, however all AEs associated with an overdose should both be entered on the Adverse Event eCRF and reported using the procedures detailed in Section 14.5.2, Reporting of Serious Adverse Events, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Endo Clinical Trial Report Form for SAEs and in an expedited manner, but should be noted as non-serious on the form and the Adverse Event eCRF.

14.6.3. Pregnancy

Subjects should be instructed to immediately notify the Investigator of any pregnancies.

Any pregnancy that occurs in a subject during this clinical study will be **reported for tracking purposes only**. All subject pregnancies that are identified during or after this study, where the estimated date of conception is determined to have occurred during study drug therapy or within 28 days of the last dose of study medication need to be reported, followed to conclusion, and the outcome reported, even if the subject is discontinued from the study. The Investigator should report all pregnancies within 24 hours using the Initial Pregnancy Report Form, and any pregnancy-associated SAE using the SAE report form, according to the usual timelines and directions for SAE reporting provided in Section 14.5.2. Monitoring of the pregnancy should continue until conclusion of the pregnancy; 1 or more Follow-up Pregnancy Report Form(s) detailing progress, and a Two-Month Follow-up Pregnancy Report Form detailing the outcome, should be submitted.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE report form. Spontaneous miscarriages should also be reported and handled as SAEs.

A subject who becomes pregnant must be withdrawn from study treatment (if applicable) and will not be eligible for retreatment while pregnant, but may remain in the study for observational purposes and may be considered for retreatment, if eligible, when no longer pregnant or breastfeeding. Attempts to obtain the pregnancy follow-up and pregnancy outcome information detailed above are necessary even if a subject discontinues treatment because of pregnancy.

14.6.4. AEs/SAEs Experienced by Non-subjects Exposed to Study Medication

Non-subjects are persons who are not enrolled in the study but have been exposed to study medication, including instances of diversion of study medication. All such AEs/SAEs occurring in non-subjects from such exposure will be reported to the Endo PVRM Department (when the non-subject agrees) on the departmental form for serious adverse experiences regardless of whether the event is serious or not. Instructions for completing the form for events experienced by non-subjects will be provided. SAEs occurring in non-subjects exposed to study medication will be processed within the same SAE reporting timelines as described in Section 14.5.2, Reporting Serious Adverse Events. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

14.7. Clinical Laboratory Determinations

Clinical laboratory tests will be conducted according to the Schedule of Events (Section 5.1 and Section 5.2). Clinical laboratory tests will be performed by a designated central laboratory. Each site will be provided with instructions on specimen collection, preparation, packaging and transport. Refer to the central laboratory manual for further information regarding sample collection, handling, and labeling. The results of the tests will be returned to the investigational sites.

Clinical laboratory test data will be reviewed by the Investigator, or designee, and additional clinical laboratory tests may be ordered at his/her discretion (eg, if the results of any clinical laboratory test falls outside the reference range or clinical symptoms necessitate additional testing to ensure safety). Any additional testing will be performed by the designated central laboratory. The Investigator or qualified designee must acknowledge the review of laboratory results.

The Investigator will review all abnormal lab results for potentially clinically important. Any abnormal clinical laboratory test result meeting the Investigator's criteria for potentially clinically important (refer to central laboratory manual) will be recorded as an AE or SAE as appropriate (see Section 14.1.1, Adverse Events, and Section 14.1.2, Serious Adverse Events).

Laboratory results will be sent electronically to Endo Pharmaceuticals Inc. for data management.

Clinical laboratory parameters that will be measured in this study are listed in Table 8.

Table 8: Clinical Laboratory Tests

Hematology	Biochemistry	Urinalysis
Hemoglobin	Glucose	Glucose
Hematocrit	Sodium	Protein
Red blood cell	Potassium	Specific gravity
White blood cell (WBC)	Calcium	pH
Platelets	Chloride	Ketones
WBC Differential	CO_2	Bilirubin
	Inorganic phosphate	Urobilinogen
	Blood urea nitrogen	Nitrite
	Creatinine	Blood*
	Creatinine clearance (estimated)	Leukocytes*
	Aspartate transaminase (AST)	
	Alanine transaminase (ALT)	
	Gamma-glutamyl transferase (GGT)	
	Total bilirubin (TBL) (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	
	Uric acid	

* Microscopic examination will be performed if blood or leukocytes are detected by dipstick.

For women of childbearing potential, a serum pregnancy test will be performed at the Day 71 visit from the double-blind study (EN3835-302 or EN3835-303), the results of which will be data transferred to the Screening Visit of this open-label study if the Screening Visit occurs within 14 days of the Day 71 visit of the double-blind study. Additionally, a serum pregnancy test will be performed at the Screening B visit of any Category I and/or eligible Category II subject screening for the Treatment phase of the study. Urine pregnancy tests will be performed at the other study visits (refer to Section 5.1 and Section 5.2). If necessary, additional urine pregnancy tests can be performed at any time during the study at the discretion of the Investigator. Urine pregnancy test kits will be supplied by the Sponsor.

14.8. Anti-AUX-I and Anti-AUX-II Antibodies

Serum samples will be collected and will be tested for binding anti-AUX-I and anti-AUX-II antibody testing at the visits designated in Section 5.1 through Section 5.4. For Category I subjects and/or eligible Category II subjects receiving retreatment, a subset (based on every other sample from the Treatment Visit 4 upper and lower quadrants of binding antibody titers) of subject samples will be tested for neutralizing antibodies from these visits; additional samples will be retained.

The serum samples obtained will be processed, stored and then shipped on dry ice to the designated central clinical laboratory before forwarding to Endo's appointed laboratory for the determination of anti-AUX-I and anti-AUX-II antibodies according to the laboratory manual.

14.9. Vital Signs

Vital sign measurements will be documented as described in each of the Schedule of Events (Section 5.1 and Section 5.2). These parameters include pulse rate, respiratory rate, systolic and diastolic blood pressure, and body temperature. Pulse and blood pressure readings will be taken after the subject has been sitting for 5 minutes.

The Investigator will review all vital sign values for clinical significance prior to discharge. Any vital sign value meeting the Investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see Section 14.1.1, Adverse Events, and Section 14.1.2, Serious Adverse Events).

For eligible Category I and Category II subjects receiving retreatment, vital signs will be assessed at the time points shown in Table 9 after the subject has rested for at least 5 minutes.

Table 9: Vital Signs Measurements on Injection Day

Time Point Relative to Last Injection	Blood Pressure, Respiratory Rate, and Pulse Rate	Body Temperature
Up to 4 hours (before treatment)	X	X
Approximately 15 minutes after	X	
Approximately 30 minutes after	X	X

14.10. Electrocardiogram

Performing a 12-lead electrocardiogram (ECG) is not necessary if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-302/303).

If the date of Screening B visit is later than 12 months since obtaining the ECG in study EN3835-302/303, subjects will have a resting 12-lead ECG performed during the Screening B visit.

A qualified physician will interpret, sign, and date the ECGs. Electrocardiogram assessments must be "within normal limits" or interpreted as "abnormal, not clinically significant" for the subject to be included in the study.

Any ECG result meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see Section 14.1.1, Adverse Events and Section 14.1.2, Serious Adverse Events).

14.11. Physical Examination

A complete physical examination will be performed at the double-blind Day 71/Screening Visit and at additional Visits as designated in Section 5.1 and Section 5.2. All examinations will be performed by a physician or health care professional listed on the Form FDA 1572 and licensed to perform physical examinations. Height and body weight will be measured and recorded at screening and at designated visits where physical exams are to be conducted. Height and body weight will be measured at additional visits for Category I and retreatment-eligible Category II subjects (in the absence of a full physical exam) as designated in Section 5.2.

The Investigator will review all physical exam findings for clinical significance. Any physical exam finding meeting the Investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see Section 14.1.1, Adverse Events and Section 14.1.2, Serious Adverse Events).

14.12. Other Safety Assessments

Not applicable.

15. ASSESSMENT OF PHARMACOKINETICS

Not applicable.

16. ASSESSMENT OF PHARMACODYNAMICS

Not applicable.

17. STATISTICAL CONSIDERATIONS AND METHODS

17.1. Determination of Sample Size

Approximately 420 active subjects who completed the EN3835-302/303studies will rollover to this study. This sample size should be adequate to determine long-term safety and TRR to EN3835.

17.2. Subject Populations

For subjects entering the open-label study period, subjects who received active EN3835 in their double-blind study (EN3835-302/303) will be classified into one of three categories:

Category I: 1-Level Composite Responders

Category II: 2-Level Composite Responders

Category III: Non-Composite Responders

Based on subject category, three (3) populations are considered in the statistical analysis of the study: overall safety population, Day 180 Observational Population, and Time to Reduction in Response (TRR) Population.

17.2.1. Overall Safety Population

The overall safety population is defined as all subjects who enter the open-label study period and received EN3835 in EN3835-302 or EN3835-303. This population will include all Category I, II, and III subjects. All safety analyses will be based on this population. In addition, the safety data will be summarized separately prior to retreatment and after the retreatment period.

17.2.2. Day 180 Observational Population

The Day-180 observational population will include all rollover subjects from studies EN3835-302/303. The safety analysis for the data obtained from Screening to Day 180 will be based on this population.

17.2.3. Time to Reduction of Response (TRR) Population

The TRR population is defined as all subjects who have at least a 1-level or 2-level improvement in both CR-PCSS and PR-PCSS ratings during the double-blind study or open label study (for retreated subjects) for either/both treated buttocks. This population will include Category I and II subjects. TRR will be evaluated separately for subjects who had a 1-level and 2-level composite improvement in CR-PCSS and PR-PCSS during studies in each buttock. The efficacy data will be summarized separately for ‘prior to retreatment’ and ‘after the retreatment period.’

17.3. Subject Disposition

The number of subjects included in each study population will be summarized. The number and percentage of subjects completed and discontinued will be presented. Reasons for discontinuation as recorded on the eCRF will be summarized (number and percentage) for all subjects.

17.4. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics, including age, race, and baseline values will be summarized for each study population. The descriptive statistics will include the number and percentage for categorical response variables and number, mean, standard deviation, minimum, and maximum for continuous variables.

17.5. Efficacy Analyses

Cellulite (efficacy) assessments include:

- PR-PCSS: patient reported 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite).
- CR-PCSS: clinician reported 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite).
- PR-CIS: patient reported cellulite impact scale to assess the visual and emotional impact of cellulite (happy, bothered, self-conscious, embarrassed, looking older or looking overweight or out of shape) using a 6-question survey, with each question rated from 0 (not at all) to 10 (extremely). A PR-CIS total score and an abbreviated PR-CIS score (excluding question 5) will be derived from these 6 individual questions.
- Subject Global Aesthetic Improvement Scale (S-GAIS): a 7-level scale ranging from 3 (very much improved) to −3 (very much worse).
- Subject Satisfaction With Cellulite Treatment Assessment: a 5-point scale ranging from +2 (very much satisfied) to −2 (very much dissatisfied).
- Subject Self-Rating Scale (SSRS): a 7-level scale that ranges from 0 (extremely dissatisfied to 6 (extremely satisfied).

All cellulite assessments will be performed on each individual treatment area. Treatment areas will be evaluated separately.

Efficacy analyses may be performed at any time point determined to be necessary by the Sponsor.

17.5.1. Analyses

The analyses of cellulite assessments will be based on the TRR population(s). The TRR will be defined from time of assessing the efficacy (ie, Day 71 at EN3835-302/303, or Day 71 in the retreatment period) to the study visit at which a composite 1-level reduction of response in both PR-PCSS and CR-PCSS is observed.

The defined endpoints will include:

- Proportion of subjects with reduction of response:
  - Proportion of subjects with both CR-PCSS and PR-PCSS ratings worsening 1-level compared to their corresponding score at Day 71 in the studies.

  - Proportion of subjects with both CR-PCSS and PR-PCSS ratings back to their baseline (Day 1 of the double-blind study) or worse.
  - Proportion of subjects with both CR-PCSS and PR-PCSS ratings worsening 2-levels compared to their corresponding score at Day 71 in the studies.
  - Proportion of subjects with either CR-PCSS or PR-PCSS ratings worsening 2-levels compared to their corresponding score at Day 71 in the studies.
- Proportion of subjects at each level of improvement in the PR-PCSS.
- Proportion of subjects at each level of improvement in the CR-PCSS.
- Changes in the PR-CIS total scores from baseline.
- Proportion of subjects at each level of improvement in the S-GAIS.
- Proportion of subjects at each level of improvement in Subject Satisfaction with Cellulite Treatment.
- Proportion of subjects at each level of improvement in the SSRS.

All results for each endpoint based on the collection time points as described in Section 5.1 through Section 5.3 will be derived and summarized by treated area, subject category, and study visit (day) using appropriate descriptive statistics. The baseline or reference data point will be detailed in the Statistical Analysis Plan (SAP).

17.6. Safety Analyses

The following variables are safety endpoints.

- AEs: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
- Injection site reactions/local tolerability in treatment area (through subject and Investigator reporting)
- Vital signs
- Laboratory testing

AEs will be summarized by treatment exposure category, ie, initial exposure to EN3835 in EN3835-302/303 versus re-exposure to EN3835 in this open-label study (EN3835-304) using descriptive statistics.

17.6.1. Prior, Concomitant, and Follow-up Medication

The World Health Organization (WHO) Drug Dictionary will be used to classify prior and concomitant medications by therapeutic class. The version used in this study will be stated in the Data Management Plan. Prior medication will be defined as any medication with a start date prior to the study start reference date. Concomitant medication is defined as any medication with a start date on or after the study start reference date or reported as ongoing. Any medications started after the last dose of study drug will be considered as follow-up medications.

Prior and concomitant medication use will be summarized descriptively by the number and percentage of subjects receiving each medication within each therapeutic class. Multiple use of the same medication by a subject will be counted only once.

17.6.2. Study Drug Exposure

For those subjects that elect, are eligible, and do receive retreatment, the number of injections per treatment area (buttock) and in total will be summarized by counts and percentages. The number of dimples per treatment area (buttock) treated will be summarized with counts and percentages.

17.6.3. Adverse Events

The MedDRA dictionary will be used to code AEs. The version used in this study will be stated in the Data Management Plan.

Descriptive statistics (the number and percentage) for subjects reporting TEAEs will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug.

SAEs and AEs leading to premature discontinuation of study drug will be summarized. Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation, and subjects who die (if any).

17.6.4. Vital Signs

Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and body weight) and their changes from baseline at each visit and at the end of treatment visit will be presented.

Vital sign values are potentially clinically important (PCI) if they meet both the observed value criteria and the change from baseline criteria. The criteria for PCI vital sign values will be detailed in the SAP. A listing of all AEs for subjects with PCI vital signs will also be provided.

17.6.5. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline will be presented for each clinical laboratory parameter.

The number and percentage of subjects with PCI post-baseline clinical laboratory values will be tabulated. The criteria for PCI laboratory values will be detailed in the SAP. A listing of all subjects with PCI laboratory values will also be provided.

17.7. Immunogenicity Analyses

Immunogenicity variables include anti-AUX-I/anti-AUX-II binding antibody results. Binding antibody levels will be determined from samples collected on scheduled visits (see Section 5.1 through Section 5.4).

Descriptive statistics (percent of positive measurements and average antibody level) will be presented for anti-AUX-I and anti-AUX-II antibody levels at each time point by treated area and by treatment exposure category. Average antibody levels will be summarized on logarithmically transposed titer values.

In addition, a subset of subjects' samples with anti-AUX-I and anti-AUX-II neutralizing antibodies will be summarized using appropriate descriptive statistics.

17.8. Pharmacokinetic Analyses

Not applicable.

17.9. Pharmacodynamic Analyses

Not applicable.

17.10. Other Data (eg, Health Economics/QOL, Pharmacogenetic, etc)

Not applicable.

17.11. Interim Analysis

No interim analysis is planned for this study.

17.12. Statistical Software

Statistical analyses will be performed using Version 9.3 (or higher) of SAS® (SAS Institute, Cary, NC).

18. STUDY DRUG MATERIALS AND MANAGEMENT

18.1. Study Drug Identity

EN3835 is manufactured and supplied by Endo.

EN3835 is a sterile lyophilized powder consisting of 0.92 mg of collagenase clostridium histolyticum, 18.9 mg sucrose, 1.1 mg Tris, 37.7 mg mannitol, and hydrochloric acid qs to pH 8.5.

EN3835 sterile diluent for reconstitution is 0.6% sodium chloride and 0.03% calcium chloride in water for injection.

18.2. Study Drug Packaging and Labeling

Each vial of study drug and diluent will minimally be labeled with contents, Sponsor identification, storage, administration/use, and appropriate cautions statements; additionally, study drug will be labeled with kit number. Each kit will contain one vial each of EN3835 and sterile diluent.

18.3. Study Drug Storage

All study drug will be provided by Endo. Study drug must be stored in an appropriate, secure area. Study drug must be kept in a temperature-monitored refrigerator (2°C-8°C) with locked access until used or returned to Endo.

18.4. Study Drug Preparation

Refer to the Reconstitution Instructions for detailed preparation instructions.

For each dose session, the interactive web response system (IWRS) will dispense 1 kit. Eight 0.9-mL syringes will be prepared from each vial of EN3835, 8 syringes/kit (in the case of 2 qualifying buttocks). If only 1 qualifying buttock, only four 0.9-mL syringes will be prepared from each vial of EN3835, with the remainder of the reconstituted unused study drug solution stored in a secure location until reconciled and returned by the Clinical Research Associate.

Used drug vials should be returned to the kit carton and stored in a secure location until reconciled and returned by the Clinical Research Associate (CRA). Dispose of used needles and syringes per local regulations.

The reconstituted study drug solution should be administered as soon as possible after reconstitution. The study drug solution can be kept at room temperature for up to 4 hours following the start of the reconstitution process. If more time is needed prior to injection, refrigerate the reconstituted drug vial for up to 24 hours. Remove reconstituted drug vial from the refrigerator and allow it to stand at room temperature for 15 minutes prior to preparing the administration syringes and injection of study drug.

18.5. Study Drug Accountability

A drug inventory form must be kept current by the site staff designated to be responsible for reconstitution and must be made available to the clinical monitor, Endo employees, IRB/IEC, and regulatory agencies for routine inspection and accountability during monitoring visits. When instructed by Endo, the Investigator agrees to return all original used or unused study drug kits to Endo's return vendor.

18.5.1. Study Drug Handling and Disposal

The Investigator agrees not to supply study drug to any person except to those subjects enrolled in the study. The Investigator is responsible for recording the receipt and use of all drugs supplied and for ensuring the supervision of the storage and allocation of these supplies. All used and unused study drug will be returned, and unit counts will be performed whenever medication is returned. The site must account for all study drug received and its use. At the end of the study, all used drug and unused kits will be returned to Endo's return vendor.

19. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

19.1. Source Documents

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This study allows for direct data entry (DDE) for selected data points as outlined below:

- PR-PCSS
- CR-PCSS
- S-GAIS
- PR-CIS
- Subject Satisfaction with Cellulite Treatment
- SRSS

All other data points, at a minimum, should have supporting source documentation for entries in the eCRF.

19.2. Study Monitoring

A representative of Endo Pharmaceuticals Inc. will meet with the Investigator and his/her staff prior to the entrance of the first subject to review study procedures and methods of recording findings in the eCRF.

After enrollment of the first subject, an Endo Pharmaceuticals Inc. representative will be assigned to periodically monitor each Investigator site for study progress and to verify that standards of Good Clinical Practice (GCP) were followed. The Investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed eCRFs, signed consent forms and other study related documents are readily available for review.

19.3. Audits and Inspections

The Investigator shall permit audits and inspections by the Sponsor, its representatives and members of regulatory agencies. The Investigator should immediately notify the Sponsor of an upcoming FDA or other regulatory agency inspection.

19.4. Institutional Review Board (IRB)

The Investigator shall permit members of the IRB/IEC to have direct access to source documents.

19.5. Data Recording and Documentation

All data recordings and source documentation (including electronic health records) must be made available to the Sponsor (or designee), FDA and any other regulatory agencies that request access to study records, including source documents, for inspection and copying, in keeping with federal and local regulations.

20. QUALITY CONTROL AND QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified principal investigators and appropriate study centers, review of protocol procedures with the principal investigators and associated personnel prior to start of the study, and periodic monitoring visits conducted by the Sponsor or Sponsor representative. Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigator site termination and regulatory authority notification.

The Sponsor or its designee will utilize qualified monitors to review and evaluate activities conducted at Investigator Sites.

The data will be entered into the clinical study database and verified for accuracy, following procedures defined by the Sponsor (or designee). Data will be processed and analyzed following procedures defined by the Sponsor (or designee).

The study will be monitored and/or audited at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the Study Protocol; International Conference on Harmonisation (ICH), E6 consolidated guidelines; and other applicable regulations. The extent, nature, and frequency of monitoring and/or audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. At the conclusion of a program, a compliance statement will be generated by the Sponsor (or designee) listing all audit activities performed during the clinical study.

21. ETHICS

21.1. Ethics Review

Approval by the IRB/IEC prior to the start of the study will be the responsibility of the Investigator. A copy of approval documentation will be supplied to Endo Pharmaceuticals Inc. along with a roster of IRB members that demonstrates appropriate composition (a Department of Health and Human Services [DHHS] Assurance Number will satisfy this requirement).

The study protocol, the informed consent form, advertisements, materials being provided to subjects and amendments (if any) will be approved to IRB/IECs at each study center in conformance with ICH E6, the Code of Federal Regulations (CFR), Title 21, Part 56 and any other applicable local laws. The Investigator is responsible for supplying the IRB/IEC with a copy of the current IB, Package Insert, or SPC as well as any updates issued during the study. During the course of the study, the Investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB/IEC of SAEs or other significant safety findings, per the policy of the IRB/IEC. At the conclusion of the study, the Investigator will submit a final report or close out report to the IRB/IEC and provide a copy to Endo Pharmaceuticals Inc.

Any amendment to this protocol will be provided to the Investigator in writing by Endo Pharmaceuticals Inc. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB and the signature page, signed by the Investigator, has been received by Endo Pharmaceuticals Inc. Where the protocol is amended to eliminate or reduce the risk to the subject, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment and approval obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the subject, and must be immediately reported to Endo Pharmaceuticals Inc.

The Investigator will be responsible for supplying updated safety and/or study information to study subjects as it becomes available.

21.2. Ethical Conduct of the Study

This clinical study is designed to comply with the ICH Guidance on General Considerations for Clinical Trials (62 FR 6611, December 17, 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (62 FR 62922, November 25, 1997), Good Clinical Practice: Consolidated Guidance (62 FR 25692, May 9, 1997) and 21 CFR parts 50, 54, 56 and 312.

The study will be conducted in full compliance with ICH E6, the FDA guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki defined in 21 CFR, 312.120.

21.3. Subject Information and Consent

Subjects, after having the study explained to them and an opportunity to have their questions answered sufficiently, will give voluntary and written informed consent (in compliance with ICH E6, 4.8 and 21 CFR Parts 50 and 312) before participating in any study-related procedures. The

consent shall be written in a language understandable to the subject. Subjects unable to read (illiterate) shall have the consent process performed in the presence of an independent witness who shall also sign the consent. Each subject will read, assent understanding, and sign an instrument of informed consent after having had an opportunity to discuss the study and consent documents with the Investigator before signing, and will be made aware that she may withdraw from the study at any time.

In addition to obtaining informed consent/assent, the Investigator is responsible for obtaining any additional documentation to demonstrate compliance with local privacy laws applicable to activities performed.

The consent/assent process shall be recorded in source documents. Signed copies of the informed consent and/or assent will be given to the Subject/LAR and originals will be placed in the Investigator study files.

The unique subject identification number will be carried over from the double-blind, placebo-controlled study (EN3835-302/303).

22. DATA HANDLING AND RECORDKEEPING

22.1. Data Collection

Endo will provide an electronic data capture (EDC) system for this study. Data collection will involve the use of an EDC system to which only authorized personnel will have access. The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement for a user ID and password to enter or change data. The level of access to the EDC system will be dependent on the person's role in the study.

Study data will be collected from source documents and entered into an eCRF within the EDC system. The Investigator will be responsible for ensuring the eCRFs are completed in a timely manner relative to the subject's visit. In addition to periodic monitoring occurring within the system by a Sponsor monitor, programmatic edit checks will be used to review EDC data for completeness, logic, and adherence to the study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study sites and closed electronically by the monitor, data management staff or authorized staff at the study site. Additionally, the Investigator will review eCRFs, ensure all missing or corrected data is provided and will sign the eCRF pages with an electronic signature.

An electronic audit trail will be maintained in the EDC system to track all changes made to data entered in the eCRF. Data will be retrievable in such a fashion that all information regarding each individual subject is attributable to that subject. Unless otherwise indicated, all data captured in the eCRF must first be captured in source documents. Data that can be directly recorded in the eCRF will be clearly identified in the section(s) of the protocol that describes the assessment(s).

Data entries will be corrected by changing the entry in the EDC system. Any changes or corrections to eCRF data will be electronically tracked and will include the reason for correction, who made the correction and the date/time stamp when the correction was made within the audit trail of the EDC system.

In addition, any contact with the subject via telephone or other means that provide significant clinical information must be documented in source documents as described above.

22.2. Study Documentation

Upon study completion, the Investigator will be provided with complete electronic copies of the case report form (CRF) data for his/her files.

23. REPORTING AND PUBLICATION

All data generated in this study are the property of Endo Pharmaceuticals Inc. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and Endo Pharmaceuticals Inc.

24. INVESTIGATOR OBLIGATIONS

24.1. Regulatory Documents

The Investigator is responsible for creating and/or maintaining all study documentation required by 21CFR 50, 54, 56 and 312, ICH, E6 Section 8, as well as any other documentation defined in the protocol or the Investigator Agreement. The Investigator must maintain the documentation relating to this study and permit Endo Pharmaceuticals Inc. or a member of a regulatory agency access to such records.

The Investigator must provide the following key documents to Endo Pharmaceuticals Inc. prior to the start of the study:

- A completed and signed Form FDA 1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised Form FDA 1572 must be completed and returned to Endo Pharmaceuticals Inc. for submission to the FDA. For studies executed outside the United States, documentation required by the governing regulatory authority may be substituted for the Form FDA 1572.
- A fully executed contract
- The Investigator's Statement page in this protocol signed and dated by the Investigator and any subsequent amendment signature pages
- The IB acknowledgment of receipt page
- Curricula vitae for the Principal Investigator and all sub-Investigators listed on Form FDA 1572, including a copy of each physician's license (if applicable)
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals or shorter intervals defined by the IRB/IEC. All subsequent modifications must be submitted and approved by the IRB, as described in Section 21.1
- A copy of the IRB/IEC-approved informed consent form
- A list of IRB/IEC members or DHHS Assurance Number
- Laboratory certifications and normal ranges (if local labs are required by the protocol)
- A financial disclosure agreement completed and signed by the Investigator and all sub-Investigators listed on Form FDA 1572. Investigator site staff that submitted an initial financial disclosure are also responsible for informing Endo Pharmaceuticals

Inc. of any changes to their initial financial disclosure form 1 year after the completion of the study

A complete list of required regulatory documents will be supplied by Endo Pharmaceuticals Inc. or its representative.

24.2. Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff has been properly trained on the protocol and their assigned study responsibilities.

24.3. Medical Care of Study Subjects

The Investigator and/or a qualified sub-Investigator shall be responsible for the subjects' medical care. Any unrelated medical condition discovered during the course of the study should be communicated to the subject so that they may seek appropriate medical care. The Investigator will report all AEs as required by the protocol (Section 14.5). The Investigator will inform study subjects of new information regarding the study drug as it becomes available.

24.4. Use of Investigational Materials

The Investigator will acknowledge that the study drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Principal Investigator or sub-Investigators listed on Form FDA 1572 (or other regulatory document, depending on region). Study drug must be stored in a safe and secure location. At study initiation, a representative from Endo Pharmaceuticals Inc. will inventory the study drug at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. Endo Pharmaceuticals Inc. or its representative will supply forms to document total inventory as well as subject specific accountability. The Investigator is responsible for monitoring subject's use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Endo Pharmaceuticals Inc. or its designee.

24.5. Retention of Records

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study (eg, informed consents, laboratory reports, source documents, study drug dispensing records) for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an

application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation

Endo Pharmaceuticals Inc. will notify Investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by Endo Pharmaceuticals Inc. that the entire clinical investigation (not merely the Investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application (IND)/Clinical Trial Authorization (CTA) or request for marketing approval (New Drew Application [NDA]/Marketing Authorization Application [MAA]).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Endo Pharmaceuticals Inc. must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with Endo Pharmaceuticals Inc.

24.6. Subject Confidentiality

All subject records submitted to Endo Pharmaceuticals Inc. or its designee will be identified only by initials and subject number. Subjects' names are not to be transmitted to Endo Pharmaceuticals Inc. The Investigator will keep a Master Subject List on which the identification number and the full name, address, and telephone number of each subject are listed. It is the Investigators' responsibility to inform study subjects that representatives of the Sponsor, FDA, or other regulatory agencies may review all records that support their participation in the study. The Investigator will adhere to all privacy laws to which he/she is subject.

25. TERMINATION OF STUDY

The Sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

26. INVESTIGATOR'S STATEMENT

I agree to conduct the study in accordance with the protocol, and with all applicable government regulations and Good Clinical Practice guidance.

_____ _____/_____/_____

Investigator's Signature Date

_____

Typed Name of Investigator

27. REFERENCES

1. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part I. Pathophysiology. *J Am Acad Dermatol* 2010;62(3):361-70.
2. Hexsel D, de Oliveira Dal'Forno T, Mazzuco R. Definition, clinical aspects, classifications, and diagnostic techniques. In: Goldman MP, Hexsel D, eds. *Cellulite: Pathophysiology and Treatment.* 2nd ed. New York, NY: Informa Healthcare; 2010:13-21.
3. Rawlings AV. Cellulite and its treatment. *Int J Cosmetic Sci.* 2006;28(3):175-90.
4. Terranova F, Berardesca E, Maibach H. Cellulite: nature and aetiopathogenesis. *Int J Cosmetic Sci.* 2006;28(3):157-67.
5. Avram MM. Cellulite: a review of its physiology and treatment. *J Cosmet Laser Ther.* 2004;6(4):181-5.
6. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part II. Advances and controversies. *J Am Acad Dermatol* 2010;62(3):373-84.
7. Collis N, Elliot LA, Sharpe C, Sharpe DT. Cellulite treatment: a myth or reality: a prospective randomized, controlled trial of two therapies, endermologie and aminophylline cream. *Plast Reconstr Surg*. 1999;104(4):1110-4.
8. Hexsel DM, Mazzuco R. Subcision: a treatment for cellulite. *Int J Dermatol.* 2000;39(7):539-44.
9. Boyce S, Pabby A, Chuchaltkaren P, Brazzini B, Goldman MP. Clinical evaluation of a device for the treatment of cellulite: Triactive. *Am J Cosmet Surg*. 2005;22:233-7.
10. DiBernardo BE. Treatment of cellulite using a 1440-nm pulsed laser with one-year follow-up. *Aesthet Surg J.* 2011;31(3):328-41.
11. Investigational Brochure: Collagenase Clostridium Histolyticum for Injection (AA4500/EN3835), Version 7.0. Endo Pharmaceuticals Inc.; May 2016.

APPENDIX A. DOCUMENTS REQUIRED PRIOR TO INITIATION OF THE STUDY

As a sponsor of a clinical study, Endo Pharmaceuticals Inc. has an obligation to ensure that the study will be conducted by a qualified Investigator with sufficient resources of time, personnel, and physical facilities to conduct the study and to ensure that the Investigator understands and agrees to comply with the protocol, applicable regulations, policies, and procedures. The following documentation is required:

From the Principal Investigator

1. A signed agreement to perform the study per protocol (the signature page will suffice).
2. A signed Letter of Financial Agreement (including confidentiality statement).
3. Name(s) of the Principal Investigator and of all sub-Investigator(s)
4. All address(es) of the clinical site(s).
5. A current medical license valid where he/she practices and a current curriculum vitae for the Principal Investigator (signed and dated) and all sub-Investigators, to contain at least the following elements:
   a. For physicians:
      i. Date of degree in Medicine
      ii. Name of the Institution granting the degree in Medicine
      iii. Previous clinical postings with dates
   b. For non-physician allowed by national law or regulations to act as clinical Investigators:
      i. Date and description of most advanced degree
      ii. Name of the Institution granting the degree in number (i)
      iii. Other accreditation or qualifications relevant to the study
      iv. Previous postings with dates
      v. Name and qualification (see 5a above) of the physician or dentist in charge of study subjects

   NOTE: If a non-physician is serving as Principal Investigator, then a qualified physician must be assigned as a sub-Investigator for the trial, to be responsible for all trial-related medical decisions.
6. Written notification of Institutional Review Board/Independent Ethics Committee/Human Research Ethics Committee (IRB/IEC/HREC) approval. The minimum requirements are as follows:
   a. Dated letter, including:
      i. The date on which the meeting for the review of the study protocol took place
      ii. Study protocol/amendment number, and version date
      iii. A clear statement of approval of the protocol and the informed consent text with version date, and authorization for the study to proceed

iv. If the Investigator or any sub-Investigator is a part of the IRB/IEC/HREC Review Board, assurance that the Investigator abstained from voting at the meeting(s) when the study was discussed.

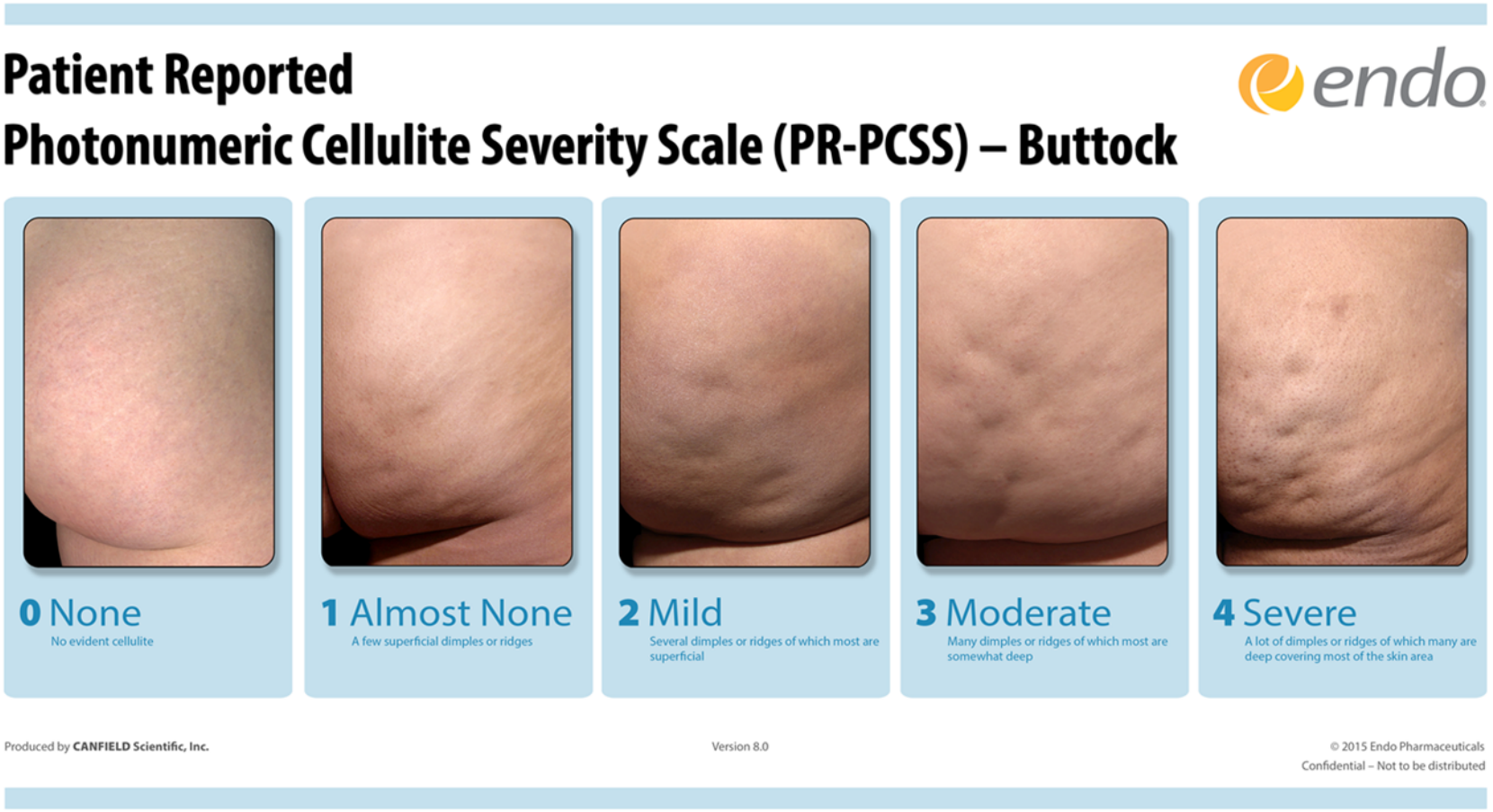
b. A dated list of the members and their occupations
c. A specimen copy of the Committee-approved informed consent text to be used in the study

7. Food and Drug Administration (FDA) Form 1572 (for studies submitted under a US Investigational New Drug application [IND]).
8. Financial Disclosure Certification or Certification of Non-Disclosure (for studies to be submitted for a US New Drug Application/Biologics License Application [NDA/BLA]).

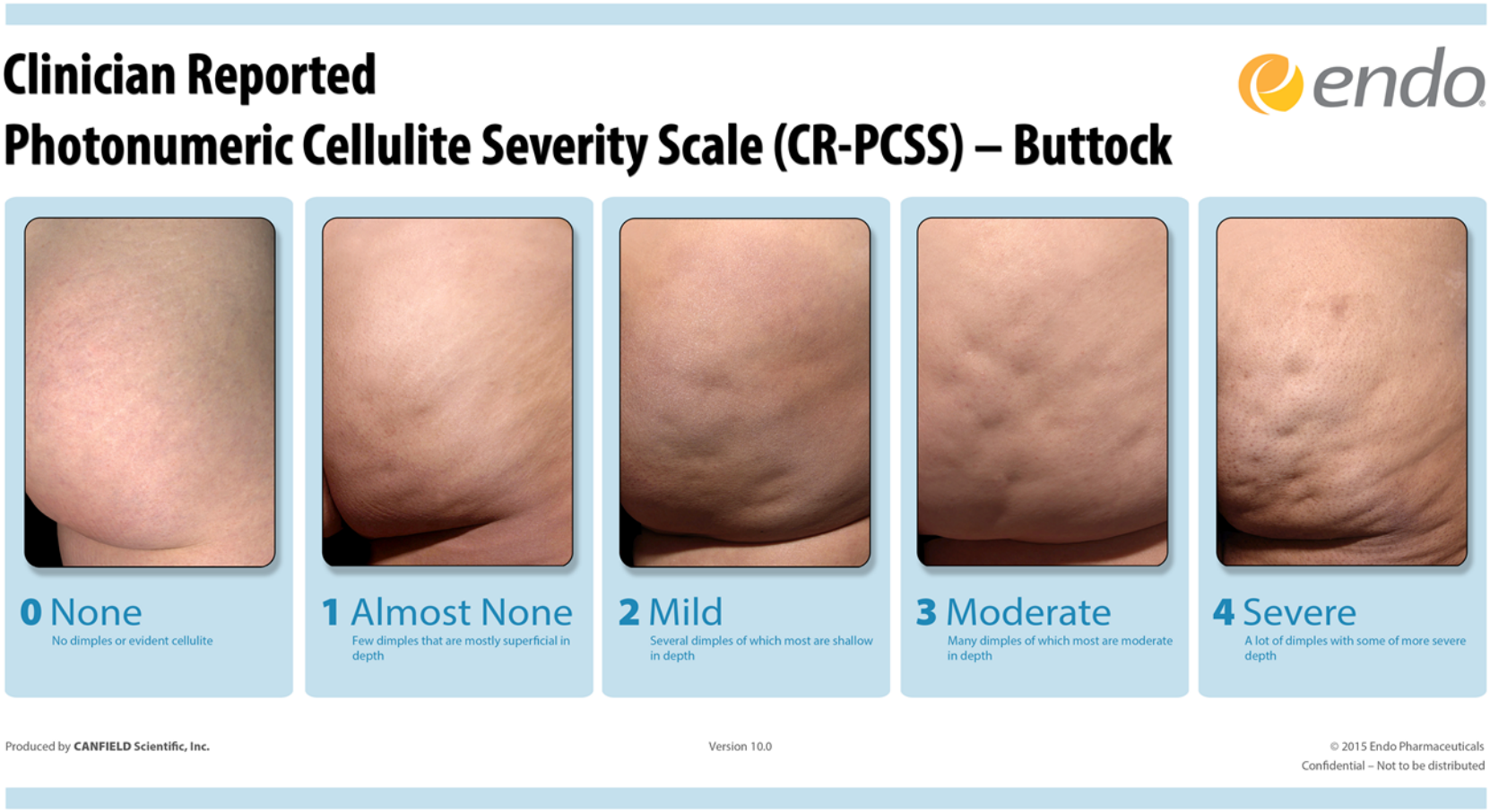
Other

Any other documentation required by national law or regulations to be in the possession of the sponsor or the Investigator for study participation or study initiation.

APPENDIX B. PATIENT REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (PR-PCSS) FOR THE BUTTOCK



APPENDIX C. CLINICIAN REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (CR-PCSS) FOR THE BUTTOCK



APPENDIX D. PATIENT REPORTED CELLULITE IMPACT SCALE (PR-CIS)

Please select the rating that best represents your answer on a scale of 0 to 10 with 0 representing "Not at all" and 10 representing "Extremely" while viewing digital images of your buttocks. Please answer each question.

1. Thinking about the areas selected for treatment, how happy are you with the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

2. Thinking about the areas selected for treatment, how bothered are you by the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

3. Thinking about the areas selected for treatment, how self-conscious are you about the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

4. Thinking about the areas selected for treatment, how embarrassed are you about the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

5. Thinking about the areas selected for treatment, how much older do you look because of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

6. Thinking about the areas selected for treatment, how overweight or out of shape do you look because of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10